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"DYSPITUITARISM": TWENTY YEARS LATER

WITH SPECIAL CONSIDERATION OF THE PITUITARY ADENOMAS

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While so much that is new and important is being accomplished by younger men, it is a great compliment to be asked a second time to deliver one of these lectures; and in venturing to address you again on the same topic as before, I can only plead that in spite of unavoidable and often protracted interruptions, it has continued to engage much of my time and thought. Were every lecturer made to understand that after the lapse of twenty years he would be requested by the Society to give an accounting of his original thesis to see what, if anything, it had amounted to in the interim, such a program would, to say the least, foster conservatism of statement at his inaugural appearance.

At a meeting of the Society on December 10, 1910, under the title "Dyspituitarism," the attempt was made to throw some light on an obscure subject—the disorders of pituitary function—then of interest to few. Of that address, which I have forced myself to reread, the less said the better. It was soon amplified into a book, long since washed away in the ever increasing flood of hypophysial literature, now pouring over the dam, and to which all departments of medicine in clinic and laboratory are adding their quota.

I scarcely recall what first led us, soon after the opening of the Hunterian Laboratory in Baltimore in 1905, to attack such an unpromising problem.* It had its surgical aspects, to be sure, in that all pituitary

The Harvey Society Lecture, as given in part, Jan. 19, 1933, at the New York Academy of Medicine.

* Alfred Fröhlich and I had been co-workers in Sherrington's laboratory in Liverpool in 1900, in which year, unknown to us, Babinski[10] had reported, under the title, "Tumor of the Pituitary Body Without Acromegaly," the case of a girl of 17, showing, at autopsy, arrested development of the organs of generation. In the following year, Fröhlich reported,[56] under an almost identical title, an example of the same syndrome in a boy of 16, the nature of the lesion not having been verified. In December, 1902, there died in Dr. Osler's wards at the Johns Hopkins Hospital a sexually undeveloped girl of 16 with the symptoms described by Babinski, and whose case was subsequently reported in my first paper which in any way pertained to the pituitary body.[33] While Babinski unquestionably is entitled to full priority in regard to this syndrome, it was popularized in Vienna through the interest aroused by the discussion of Fröhlich's paper.

disorders then known were somehow associated with tumors, but they were supposedly uncommon and because of their situation hopelessly unapproachable.

Just what might be the syndrome—if there was such a thing—of lost or impaired pituitary function was unknown. Indeed, there was no certain proof that Marie's acromegaly was not an expression of glandular deficiency. To be sure, certain states, called "adipositas cerebralis" (Schuster) and "adiposogenital dystrophy" (Bartels) had been the subject of discussion. But it seemed highly questionable whether these peculiar adiposal syndromes, which were sometimes associated with diabetes insipidus, had anything to do with the pituitary body; and whether they had any relation to acromegaly, in which malady gross hypophysial tumefactions might or might not be found after death, was still more doubtful.

Many were inclined to ascribe pituitary disorders to some perversion of secretion rather than to a quantitative loss or increase of the normal secretory product, whatever that might be—if indeed there actually was any such product in the anterior lobe. Though the belief had already been expressed by Benda[16] (1900) that hyperplasia of acidophilic elements, apparently in a stage of secretory activity and therefore representing an adenoma, was a distinctive feature of acromegaly, others (e. g., Dean Lewis[31]) described an acidophilia apparently without adenomatous delimitation. However, at the time of which I speak, pathologists took little interest in the adenopathies as such, and most of the soft cellular unaccountable enlargements of the gland were regarded as sarcomas, or the noncommittal term "struma pituitaria" was applied to them.

With our knowledge of the pituitary disorders in this chaotic state, it was learned in the course of a series of operations on the canine hypophysis that enucleation of the posterior lobe (surprisingly enough, in view of its proved pharmacodynamic properties) caused no appreciable effect, whereas in adult animals a peculiar form of fatal cachexia supervened when the entire gland was removed. The fatal issue we thought could be postponed by glandular implantations or by injection of emulsions;[31] but what was of greater significance, it was finally observed that those animals which had recovered after subtotal extirpations of the gland tended to become obese and sexually dystrophic—an experimental state comparable to adiposogenital dystrophy.[34]

And when shortly after this it was reported, first by Bernhard Aschner[7] (1910), that immature puppies not only tolerated hypophysectomy better than adult animals but remained dwarfed and sexually infantile, it was obvious that the syndrome of Fröhlich was truly a

deprivation disorder, suitably called *hypopituitarism*. This having been established, it was highly probable, all things considered, that acromegaly must represent the counter state of *hyperpituitarism;* indeed, one or two partly successful operations for acromegaly had led to an apparent amelioration of symptoms shown by a shrinkage of the hypertrophic hands and feet.

At the same time, it was clinically apparent that all examples of pituitary disease did not unmistakably fall in these two categories; certain adipose and sexually dystrophic adult patients with undifferentiated pituitary "strumas" might show traces of antecedent, or what has since been described as "fugitive" acromegaly,[11] while others in whom acromegalic changes had become pronounced tended in time to become fat and amenorrheic or impotent. These mixed syndromes consequently were taken to represent intermediary or overlapping states of disordered function conveniently classified as examples of *dyspituitarism*—whence the title of my former lecture.

While this conception of the pituitary disorders appeared at the time to be a satisfactory working basis, its weak points soon became apparent. Erdheim [48] had already (1904) shown that the usual tumor causing the syndrome of Fröhlich was of congenital origin, and suprasellar in situation; and since it was prone to deform the interbrain, he was led to attribute the syndrome largely to a diencephalic rather than a glandular source. On this basis, the acute cachexia as well as the more chronic adiposity and sexual dystrophy my co-workers and I had described [52] might conceivably have been due to unavoidable hypothalamic contusions produced by Paulesco's intracranial method of approaching the gland, which we had adopted.

While it was not then known that the functional interdependence of hypophysis and hypothalamus is such that they can scarcely be discussed separately,[37] nevertheless, from these early canine experiments there were glimmerings, solely from a hypopituitary or deprivation aspect, to be sure, of an important influence exercised by the anterior lobe on the factors of growth and of sex. At the same time, striking secondary changes, particularly in the thyroid gland, had been observed, together with a greatly increased tolerance for carbohydrates, which needed explanation.[60, 134]

It is incredible that from so small and unpromising an acorn there should have sprouted—or appear to have sprouted—in so short a time as twenty years such a far reaching and diversified plantation of interests. The literature of the subject in its many ramifications has become so enormous no one can pretend to keep pace with it, far less to comprehend it all in view of the contradictions and subtleties—not to say speculations—with which it has become enmeshed.

Attention has periodically switched from a consideration of the gland as a whole, to the posterior lobe, to the anterior lobe, and back again to a study of the separate properties of extracts of anterior or posterior lobe or of the tuberal cuff, and to the effect on them of hypothalamic stimulation or paralysis.

Some few have worked upstream to explore the central neuroglandular mechanisms that are involved, but a far greater number have worked downstream to examine the isolated effects of extracts on remote tissues and subsidiary organs. A fly could scarcely be cast anywhere in these waters, even by a novice at research, without hooking something deserving of experimental study; and for this purpose a goodly percentage of the animals in the ark, the amphibians below it and the doves about it have successively been utilized.

Out of all the present welter of discovery relating to the internal secretions, it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body. And should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two separable hormones of growth and sex. For these steps the brilliant experimental studies of Herbert M. Evans, on the one hand, and of Philip E. Smith, on the other, each with his several collaborators, were largely responsible.

But it is one thing to make discoveries through animal experimentation and quite another to correlate them with disease, and there is great need of an integrator to lead by the hand, through the present maze of scientific investigation, those who must deal with the victims of disordered pituitary function at the bedside. Were all human beings, male and female, as much alike as are standard rats of either sex, the clinician's difficulties might be ameliorated. Yet even rats of the purest strain show marked individual variation and fail to react precisely alike when injected with a pituitary hormone, whereas Nature's experiment of a similar kind on isolated examples of our own highly mongrel species may give results so bizarre they as yet exceed all power of interpretation.

To some of the etiologically obscure maladies that already have come to be laid at the door of pituitary dysfunction I shall have occasion to allude, and we may confidently expect that many more hitherto unexplained pathologic states will prove in time to be related to the neurobiochemical imbalance of this amazing gland. But the field is now so large it would be futile in a single address to cover more than a small corner of it; and, surmising that a consideration of the adenomas and

their effects would at this time be as likely as any other to be of general interest, I shall confine myself to this single topic.

Pituitary Adenomas.—For an understanding of these tumors we must necessarily begin with the cellular composition of that portion of the gland which Berblinger chooses to call the adenohypophysis * to distinguish it from the neurohypophysis. While much unquestionably remains to be learned of the life history of the adenohypophysial cells (by perfected stains or by methods of intravital study or artificial cultivation as yet undeveloped), in the normal adult gland only three cellular elements, as originally described by Schönemann (1892), continue to be distinguished by histologists. More properly speaking, however, they represent a single or chief element in two differing stages of activity.

This chief element, the primary mother-cell, possesses a finely granular, nonstaining (chromophobe) cytoplasm, which in the process of ripening acquires coarse secretory granules of two distinguishable types known as acidophilic and basophilic † from their peculiar reactions to dyes. What is more, these ripened cells, as Severinghaus has recently shown,[112] not only have their individually characteristic paranuclear Golgi apparatus (that of the basophilic elements being distinguished by a ring; that of the acidophils by a filamentous net), but the predetermination of the change into basophilic or acidophilic elements is actually indicated (cf. fig. 1) by the morphology of the Golgi body in the mother-cell—an important disclosure to which I shall return (cf. p. 496).

* This convenient term, occasionally used herein, permits one to escape from the awkward employment of "anterior-pituitary" as an adjective which even abbreviated to A. P. has come into common use. To the uninitiated, much of the recent German literature has become unreadable from the employment of such codes. In his recent comprehensive monograph,[21] Berblinger particularly emphasizes the functional unity of the adenohypophysis, the anatomic subdivisions of which (pars anterior, intermedia et tuberalis) he believes to be indistinguishable in man. But while this may be anatomically correct, it is physiologically embarrassing since there is every reason to believe that the neurohypophysis is activated by the enveloping portion of the adenohypophysis, and they can scarcely, therefore, be separately discussed.

† A fourth and a fifth element (the "pregnancy cells" of Erdheim and Stumme and the "castration cells" of Zacherl) are recognized, and numbers of highly similar cells are present in the gland in states of thyroid insufficiency. They all appear to be merely enlarged mother-cells which are arrested in the process of ripening through the exigencies of the physiologic state that produces them. Whether they are forerunners of acidophilic or of basophilic elements is disputed, and this may vary in different species. The nature of the Golgi bodies in the different types would probably decide the question.

The chromophobe mother-cells normally outnumber the others * and, as the character of their cytoplasm would indicate, appear to give off no secretory product, whereas the acidophilic and the basophilic elements unquestionably are in the process of elaborating, each its own peculiar active principle. We furthermore have fairly conclusive evidence that the separable growth-promoting principle is derived from the acidophilic elements, and there is some indirect evidence which suggests that the sex-maturing principle may be associated with the basophilic elements.

So far, this would seem simple enough: three distinguishable cell types—two of them actively secreting—a hormone accredited to each.

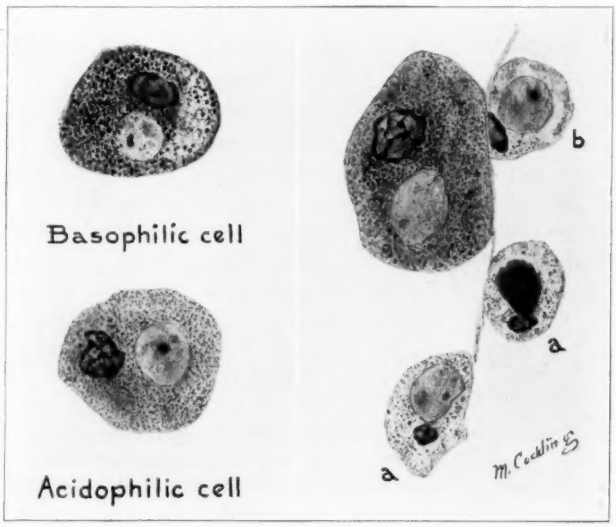

Fig. 1.—Drawing from hypophysis of monkey to show: (left) acidophilic "net" and basophilic "ring" types of Golgi, and (right) large acidophilic cell with three chromophobe elements (*b*) basophilic, (*a*) acidophilic.

But we unhappily are not permitted rest at this point, for highly competent observers are convinced that the anterior pituitary gives off several other separately identifiable hormones. This must mean either that there are more types of secreting cells in the gland than heretofore believed, or else that the ripened product of the two known types has a variable action under different circumstances. It is conceivable that

* Rasmussen [104] finds in the "normal" gland 52 per cent chromophobe, 37 per cent acidophilic and only 11 per cent basophilic cells.

the secretory product of a given cell may not always have precisely the same chemical formula, or even that a cell may discharge a cytoplasm of variable quality in different stages of ripening. But neither of these possibilities seems at all probable, and some other explanation may be forthcoming.

Now what, from a clinicopathologic standpoint, is highly significant in connection with this is the fact that only three types of pituitary adenomas are recognized: One is composed of chromophobe elements apparently identical with the nonsecreting mother-cells; in another, acidophilic elements abound, its clinical manifestations being those of overgrowth, while the third is purely basophilic in composition, its astonishing effects being conceivably ascribable to an excess of the gonad-stimulating principle. It is possible, of course, that those who have chiefly studied these pituitary adenomas have been influenced by preconceived ideas of what they should find, and there may be more types than have as yet been identified, but this appears unlikely. We, therefore, have neither cell type nor corresponding adenoma formations to represent more than three possible hormones; and the purely chromophobe adenomas, for reasons to follow, we may discard as having no secretory activity.

Adenomas of the ductless glands have long been known. To some of them processes of disease have been ascribed, but aside from the attribution of the acidophilic adenomas of the pituitary body to acromegaly and of the so-called fetal adenomas of the adenoma to hyperthyroidism, they in the past have usually been regarded by pathologists as functionally inert conglomerations of cells of no particular consequence. But a revolution in this idea has come about through the recent disclosure that a tiny adenoma of a parathyroid glandule, of pancreatic islet tissue, or of the basophilic elements of the pituitary body, represents clusters of cells in an otherwise normal organ possessing a secretory potency and activity of astonishing degree.

In fact, the experimental reproduction of a hypersecretory syndrome by the successive daily injections of a glandular extract is a feeble imitation of the uninterrupted outpouring of an excess of the natural hormone from one of these hidden pathologic "stills." No moonshiner, with every effort to throw searchers off the track, ever secreted the spot where his demoralizing product was being distilled and prepared for distribution more skilfully than Nature has done in the case, for example, of that remarkable disease, deforming osteitis fibrosa, whose gross skeletal changes von Recklinghausen fully described over forty years ago in complete ignorance of their fountain-head.

1. THE CHROMOPHOBE ADENOMAS AND THEIR SYSTEMIC EFFECTS

To most of the known adenomas of the ductless glands, like those of the thyroid, parathyroids, pancreatic islets and adrenal cortex, a hypersecretory function is now ascribed. And this, as we shall see, is true also of the acidophilic and basophilic adenomas of the anterior pituitary, whereas the more common chromophobe adenomas, to which we may first turn, appear to be an exception to the rule.

Several histologic types of chromophobe adenomas have been described,[11, 42] differing somewhat in their architecture and life history. All of them, however, are composed of cells having a nonstainable cytoplasm resembling the mother-cells, and not until they reach a size sufficient to expand the membranous and bony envelope of the gland do they produce any recognizable constitutional disorder.[65] By this time the degree of intrasellar pressure has often become such that the residual of the normal gland is peripherally so thinned out the merest traces of it can be identified on histologic sections (cf. fig. 2 *III*). The symptomatic consequences of such a slow inactivation by compression are purely hypopituitary, and the resultant adiposogenital dystrophy differs in no respect, except in its more insidious onset, from that which follows a subtotal hypophysectomy in the dog or rat, dwarfism being added to the picture if a preadolescent subject is the victim either of the disease or of the experiment.

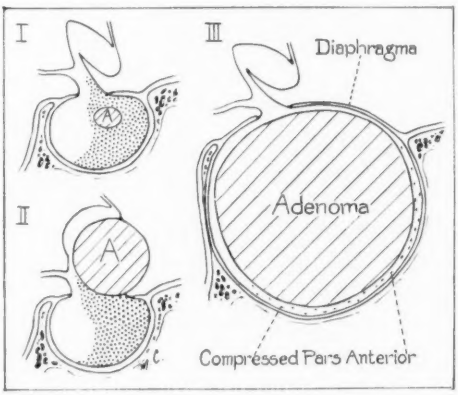

Fig. 2.—Diagrams of chromophobe adenomas (*A*) to show: *I*, small, nonsymptomatic lesion; *II*, a suprasellar lesion with chiasmal involvement but no secretory effect; *III*, an intrasellar lesion sparing chiasm but with dual hypopituitary effects from compression of glandular elements.

Operations for these chromophobe adenomas are undertaken largely to preserve vision, for the expanding lesion stretches and distorts the overlying optic chiasm. And while this has no bearing on the present topic, what does pertain to it is the fact that after one of these soft expanding tumors has been radically excavated, the compressed normal elements of the gland may, in fortunate instances, resume their functional activity. This is shown, for example, by the occasional resump-

tion of normal menstruation in women previously amenorrheic, for which there can be no other ready explanation than the release of the sex-activating cells from their pressure inhibition.*

Fragments of a chromophobe adenoma, so far as I know, have been tested only twice by implantation methods to determine the presence or absence of an active hormone, with contradictory results.† There, however, is a further reason for believing that their clinical syndrome is not attributable to a secretory product. This is based on the complete absence of any recognizable symptoms except those of chiasmal involvement [36] when one of these tumors, owing to a defective diaphragma sellae, has escaped from its intrasellar confinement and come to lie in such a position that the activity of the rest of the gland continues unimpaired (cf. fig. *2 II*).

While this argument may appear to have been unduly belabored, it seems necessary at the outset clearly to distinguish between the two actively secreting types of adenoma, subsequently to be considered, and these chromophobe tumors whose somatic effects, so far as one can determine, are purely hypopituitary.

Though the chromophobe adenomas are by far the most common type—the proportion in our series of 385 verified cases being 277 chromophobe, 107 acidophilic and "mixed," and 1 basophilic—the opportunity to study an early example post mortem has never arisen, and their more common point of origin is unknown. They vary considerably in their histologic appearance, some of them having an architecture suggesting an origin from the pars intermedia, others being structureless masses of cells in whose cytoplasm nonstainable granules suggesting secretory activity may sometimes be detected.

Whereas in the normal pituitary gland mitotic figures are not seen and are rarely if ever picked up in fixed and stained preparations of the adenomas, they occasionally may be detected on supravital preparations (cf. fig. 6). Nevertheless, these pituitary adenomas, while they may crowd their way into the cranial chamber and cause death, never seem to acquire malignant tendencies.

A few examples, possibly 2 per cent of the 385 cases, have been called adenocarcinoma by pathologists who have examined the tissues. But the fact that the patients from whom the specimens were taken, in spite of an incomplete removal of the lesion, have all survived the operation for many years belies the diagnosis of malignancy, and at the same time speaks in favor of their being composed of elements possessing no functional activity.

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* That the adiposogenital symptoms brought about by these adenomas are not ascribable to involvement of the interbrain by the enlarging tumor is evident from the fact that an associated tuberal polyuria is exceedingly uncommon and is rarely elicited by the surgical manipulations necessary to expose and remove one of them. On the other hand, polyuria *is* a common feature of hypophysial duct tumors (craniopharyngiomas), the study of which led Erdheim to advance his hypothalamic explanation of the symptoms in Fröhlich's disease. And even should polyuria not have occurred spontaneously from the effects of a growth of this kind which is more apt to be suprasellar than intrasellar in position, it is almost certain to be produced by the operative manipulations necessary for its removal.

† Kraus alludes briefly [79] to his having observed on a single test a positive follicular effect. Berblinger,[22] on the contrary, observed no effect on a single test.

Specimens removed at operation from a few of the tumors in our recent series have been studied by Dr. Severinghaus who finds: (1) that in the adenoma of acromegaly the Golgi body of all cells (fig. 3), whether chromophobe or acidophilic, is of acidophilic type; (2) that in the chromophobe adenomas the cells with a Golgi body of acidophilic type far outnumber those with a Golgi body of basophilic type. While no opportunity has arisen similarly to investigate a pure basophilic adenoma, it can readily be seen that these cytologic clues demand close pursuit.

Further studies in this direction may throw light on the composition of what Bailey and I have called [11] "mixed" (chromophobe and acidophilic, never chromophobe and basophilic) adenomas, and may enable us to determine the nature of

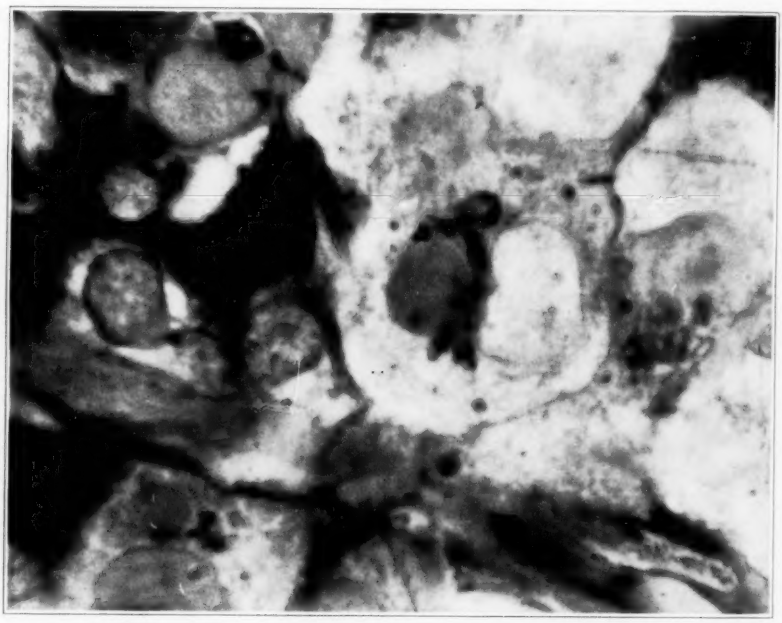


Fig. 3.—Photomicrograph of mixed adenoma (chromophobe and acidophilic) from case of "fugitive" acromegaly in which all elements have acidophilic type of Golgi net. Note large cell in center of field (magnification, × 2,400).

the enlarged chromophobe elements characterizing the gland of pregnancy, which, because of their faintly acid-staining granules, many regard as arrested acidophils.

Chromophobe adenomas, while more commonly found in adults, occasionally occur in childhood under which circumstances their dual inhibitory effect on growth-promoting and sex-maturing elements is more clear. Such a case may now be cited for purposes of illustration:

THE CASE OF EVELYN D. *A pituitary dwarf with combined intrasellar craniopharyngioma and chromophobe adenoma, twice operated on for neighborhood symptoms. Observed over a period of eight years. Recent intramuscular injections of a growth extract with symptomatic benefit but no acceleration of growth.*

Dec. 1, 1924: Admission of a 10 year old child (born Sept. 27, 1914), with headaches and impaired vision.

History.—At the age of 3, she had fallen from a piazza and cut her forehead, with no apparent ill effects. Apart from measles in her sixth year, she had been curiously exempt from the usual infections of childhood. She had been a bright and studious child who was disinclined to play with other children.

Present Illness.—A year prior to admission, she began to fall off noticeably in her school work. She was chided as being indolent, lazy and fat. Six months later, she began having troublesome headaches, became constipated and had

Fig. 4.—Expanded sella of Evelyn D. in 1924 (natural size).

attacks of vomiting. She grew sallow and lost weight in spite of her "puffy" appearance. Recently there had been a noticeable failure of eyesight.

Examination.—This showed a placid and cooperative child, definitely undersized but apparently well nourished; teeth very imperfect; height 3 feet 11½ inches (120 cm.; normal average for age, 131.5 cm.); weight 49 pounds (22.2 Kg.; normal average for age, 29 Kg.). The skin was delicate, pale and shiny suggesting a nephritic edema, but the urine was normal. The blood pressure was low, 85/45; the basal metabolic rate, — 36 per cent.

The neurologic survey disclosed a bilateral primary optic atrophy more marked on the left where vision was reduced to the perception of movements. In the right eye there was 20/70 vision with an upper temporal field defect. Roentgenograms showed a highly ballooned sella without shadows of calcification either within or above the expanded fossa (fig. 4).

Clinical Diagnosis.—Owing to the rarity of pituitary adenomas of any kind in so young a child, the typical syndrome of Fröhlich was ascribed to a probable intrasellar, uncalcified hypophysial-duct (Rathke) tumor.

Operation, Dec. 19, 1924.—Ether anesthesia. A right transfrontal exploration disclosed a chiasm and optic nerves widely spread by a bulging though intact diaphragma sellae. Suspecting a cyst, a needle was introduced, and 10 cc. of a muddy, coffee-colored fluid containing cholesterol crystals was withdrawn. The collapsed diaphragma was then incised, and a glistening sheath of tissue 2 by 3 cm. in diameter representing the cyst wall was finally dissected out. This done, a mass of soft, brownish, adenomatous tissue was brought to view, and after specimens had been taken for histologic verification, the cavity was thoroughly cleaned out by suction.

The child made a good recovery from this operation (fig. 5). Headaches ceased; vision was subjectively improved, and perimetric tests on Jan. 1, 1925, showed definite widening of field peripheries. By January 10, the fields were normal in both eyes and the visual acuity 20/20 in each. The basal metabolic rate had risen twelve points, to —24 per cent. A series of x-ray treatments was given, and she was discharged Jan. 16, 1925, greatly improved in all respects.

The Tissues.—1. The cyst wall proved to be typical of an hypophysial duct lesion. 2. The adenoma was definitely of chromophobe type.

Subsequent Notes.—For the next twenty months, the patient was lost sight of, and in response to a letter of inquiry she finally reported on Oct. 16, 1926, at the age of 12 years and 1 month. Her height was then 127.2 cm., the increment of 7.9 cm. representing a slightly subnormal increase for a twenty month interval at her age (cf. fig. 10). She weighed 58½ pounds (26.5 Kg.), an increase of 9½ pounds (4.3 Kg.). The vision in the left eye, however, had fallen off to 10/200 with return of temporal hemianopsia and central scotoma.

Two years more elapsed when, on Jan. 26, 1929, she reported with the complaint of occasional headaches with beginning loss of vision in the left eye (aged 14 years, 4 months; height, 129 cm.; weight, 28.6 Kg.). During the next twelve months the symptoms slowly increased, and finally vision became so impaired she could make no further progress at school and her guardians were induced to have her reenter the hospital for further study.

Readmission, Jan. 30, 1930.—The child, as at the time of her first admission, had become apathetic, inactive and inclined to remain in bed. Both optic disks showed a high degree of atrophic pallor. The fields showed bitemporal hemianopsia more marked on the left, with macular involvement. Vision in the left eye was for movements only; in the right eye, 20/200. The child had grown 1.6 cm. in the preceding twelve months. The basal metabolic rate was —27 per cent. The sella was definitely enlarged over the previous entry.

Second Operation, Feb. 19, 1930.—Under procaine hydrochloride anesthesia, the original flap was reelevated, and the suprasellar region reexposed without difficulty. The diaphragma sellae had reformed and was bulging between the spread arms of the chiasm; it was electrically opened, and soft adenomatous tissue immediately began to extrude. After fragments had been secured for supravital study and for fixation, the cavity was once more thoroughly cleaned out, masses of the large tumor being easily dislodged by the spoon and removed by suction; no trace of the former cyst was seen. The margins of the incised diaphragma, having been drawn away from the nerves and chiasm until they rode free, were coagulated and infolded into the great cavity which would easily have held a large olive. After complete hemostasis, closure was carried out with the usual detail.

Postoperative Notes.—The child behaved admirably during the operation, and there was no reason to expect trouble. On the late afternoon of February 20 and again on the afternoon of February 22, the flap had to be reelevated for an

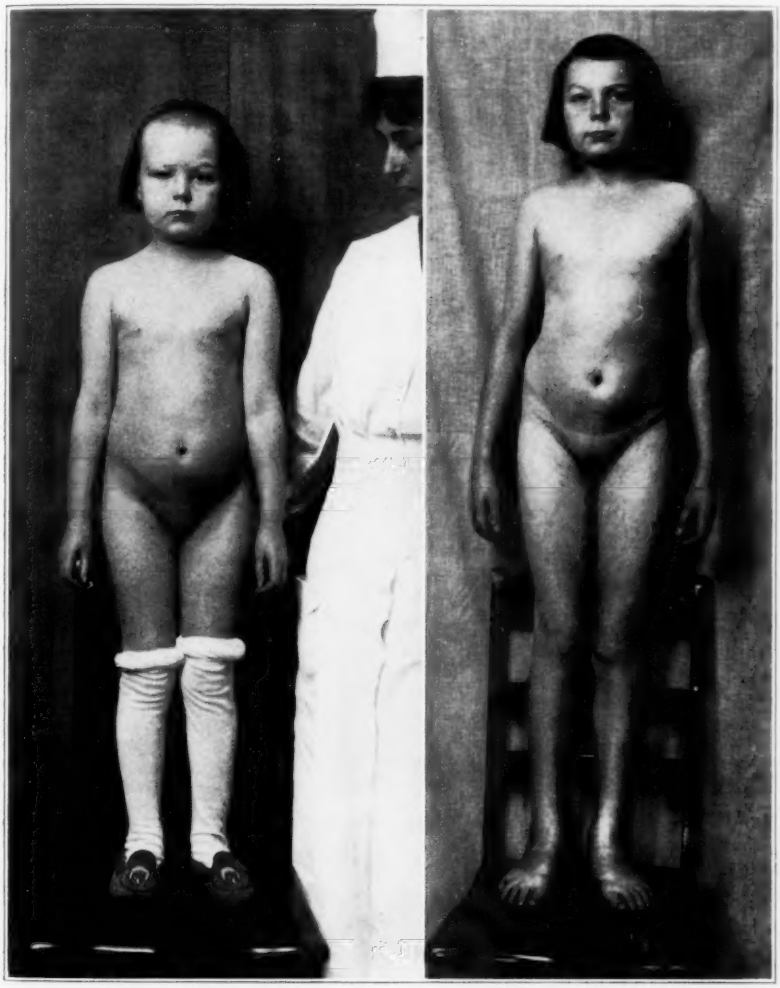


Fig. 5.—Evelyn D. (standing on same chair). Left figure, shortly after first operation, Jan. 6, 1924, aged 10 years, 3 months. Right figure, Dec. 19, 1932, aged 18 years, 3 months.

extradural clot. There meanwhile was a marked hyperpyrexia (105 to 106 F.), which fortunately soon subsided. Though these unfortunate surgical complications delayed convalescence, her visual fields rapidly widened, and by March 10 acuity

was so far regained that she was able to read small print; the main object of the operation was therefore attained. By the time of her discharge, on May 4, 1930, while more alert than she had been on admission, she was pale and bloated and had little appetence for food.

Pathologic Note.—Supravital examination: The soft tumor was easily spread. The cells were typically of the large chromophobe type with delicately granular cytoplasm and large nuclei. Occasional multinuclear cells were seen and a single mitotic figure (fig. 6). Fixed sections showed a chromophobe adenoma with considerable intercellular fibrous tissue ascribed to the former operation. No further mitoses were found.

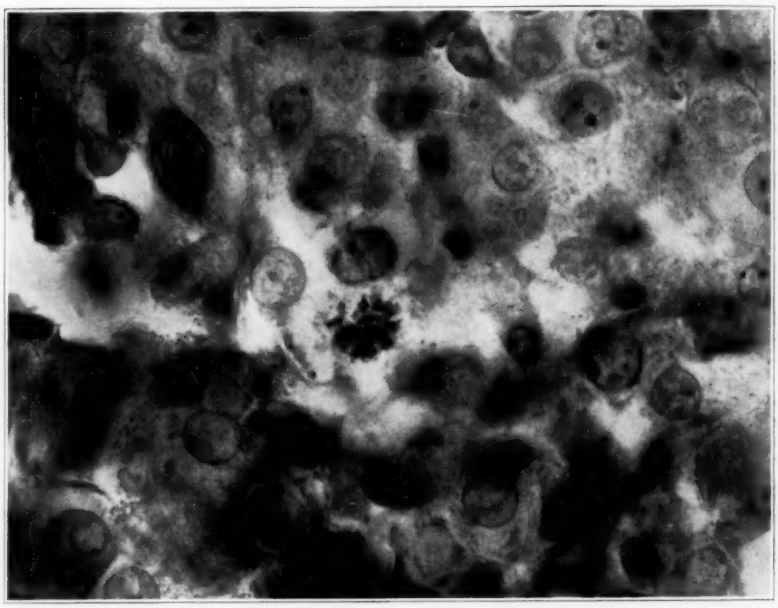


Fig. 6.—Supravital preparation of chromophobe adenoma from Evelyn D., showing mitotic figure (magnification × 850).

Third Admission, June 13, 1931.—The patient reentered the hospital on request for the annual check on her condition. There had been little if any change. She was the same prim, laconic, undersized, well behaved child, with finely wrinkled and freckled skin (fig. 7). Her age was 16 years, 9 months; weight, 30.4 Kg.; height, 132.4 cm.—a gain of 1.4 cm. in sixteen months since the operation. The basal metabolic rate was —19 per cent. It had been our intention at this time to give her injections of a newly prepared growth extract, but its excess of protein content rendered this inadvisable.

Experiences with Replacement Therapy.—Obviously what this child needed from the first was some form of effective substitution therapy, and before continuing with her story, our ineffectual experiences in

this direction may be recounted. As already mentioned, the attempt had been made in 1909 to overcome the acute postoperative cachexia that commonly follows total hypophysectomy of adult dogs, and we had even reported [31] what we thought were encouraging results following glandular implantations and the injections of crude bovine emulsions. Indeed, feeling that pituitary extracts might not be what is called species-specific, I had once transplanted the hypophysis taken from a still-born child into the brain of a man with an extreme degree of pituitary deficiency.

Fig. 7.—Evelyn D. at 18 years of age. Note persistent freckles on exposed areas of the otherwise pale skin, a characteristic of most hypopituitary cases.

This was done in accordance with Halsted's newly expressed formula [63] that glandular implantations would survive only in the presence of a physiologic deficit on the part of the host *; but the case, as it turned out, was highly unsuitable for such an experiment, the patient's critical symptoms (produced by a craniopharyngioma) having been hypothalamic rather than pituitary. The brain was selected as the

* These conclusions were based on experiences with parathyroid transplantations. Manley and Marine [87] showed a few years later that the parathyroid bodies readily survive autotransplantation in the absence of a physiologic deficit.

proper site for the transplantation on the assumption that the functioning gland required a neural environment.

Dr. Smith's subsequent success [114] (1927) in restoring immature hypophysectomized rats to a normal status by daily intramuscular implantation of fresh glands was based on the principle of absorption of what active secretion was already present in the tissue, without expectation that the implant might survive to produce more, no evidence of this ever having been observed. While it may therefore be unavailing, further efforts to secure a functioning pituitary transplant will doubtless be made, for theoretically it would provide the ideal form of substitution.

We were made acquainted with some of Dr. Evans' early methods of preparing the growth hormone by one of his pupils, Mr. Harold Teel, who entered the Harvard Medical School in 1925. In collaboration with Dr. Tracy Putnam, a neutralized, dialyzed, potent and sterile extract was prepared,[98] armed with which we proceeded to elbow our way into the problem of experimental overgrowth. The prolonged intraperitoneal administration of the substance in dogs was found to cause what was looked on as the experimental counterpart of acromegaly.[99, 17, 127]

Encouraged by the effectiveness on animals of this sterile extract, in May, 1927, Dr. Putnam gave seven successive intraperitoneal injections of 10 cc. of the substance to the minute pituitary dwarf described in another place [35] as an example of hypopituitarism due to a craniopharyngioma. Each injection caused a prompt evacuation of the bowels with vomiting, in spite of which they were continued over a week's time as they seemed definitely to improve the child's appetence and general condition. A temporary febrile reaction following the last injection, however, led to their discontinuance.

During the following year, Drs. Putnam and Teel [124] made some further improvements in their extract by salting out with sodium phosphate and succeeded in getting a potent substance which was not only sterile but reasonably free from protein. Meanwhile, much time was expended in searching for a suitable chemical assay of potency by the study of metabolism and other ways, the most promising being based on the finding by Teel and Watkins [128] of a definite drop of the nonprotein nitrogen following injections of the hormone in dogs, suggesting "mobilization from the blood of substances needed for the building up of new protoplasm."

It soon proved to be beyond the capacity of our laboratory to prepare the extract in sufficient bulk for our purposes, and Parke, Davis and Company through the agency of Dr. E. P. Bugbee kindly agreed to come to our aid. They already had marketed an anterior lobe pituitary preparation (antuitrin) which one of my co-workers, Dr. Davidoff, had tested (1924-1925) in rats without being able to detect the presence of the growth hormone, the only observed effect being an interruption of estrus. Subsequently adopting the improved Putnam-Teel procedure with some modifications in the way of a preservative,[25] they have prepared a series of substances which are sterile, give no protein reaction on injection, and contain a sufficient amount of the growth hormone to give prompt effects when tested on hypophysectomized rats.

During the summer of 1929, one of the early preparations of modified anterior lobe pituitary preparation (antuitrin-G) was tested on three pituitary dwarfs ranging from the ages of 19 to 30, all with open

epiphyses. They received daily intragluteal injections of 5 cc. without appreciable effect; and on retesting the substance on rats, it was disappointingly found to have lost its growth-stimulating effect, possibly because of the nature of the preservative added to it. A more potent anterior lobe pituitary preparation which retained its activity was subsequently prepared, and to give this a reasonable trial Evelyn D. was readmitted to the hospital.

Fourth Admission, March 7, 1932.—During the twelve months' interval, normal vision had fortunately been retained, but the patient had lost ambition, spent most of her time in bed and was too indolent to go to school. This may in part have been due to consciousness of the increasing disparity between her age—she was now 17½—and her size. While her height (cf. fig. 10) had slowly increased (from 120 to 134 cm.) in the seven years she had been under observation and her weight had perceptibly jumped after each of the operations (cf. fig. 11), even this had remained stationary for eighteen months. Her epiphyses on x-ray films still resembled those of a child of 8 or 9 years. The blood pressure remained low, 90/60; also the basal metabolic rate, — 18 per cent.

In view of the child's marked inappetence, preliminary studies were made of the calories she would normally consume on as appetizing a diet as could be provided; 964 calories was the highest she could be prevailed on to take. Meanwhile, the more potent anterior lobe pituitary preparation was tested intradermally and subcutaneously to exclude the possibility of a foreign protein reaction, and on March 16 she was given her first daily intramuscular injection of 2 cc. The effect on her appetite was immediate. Her measured calories on the second day were 1,285; on the third, 1,356; on the fourth, 1,466, and she was soon taking 1,600 calories *per diem*. Meanwhile, her appearance and activity were noticeably improved.*

The injections, which were continued for one hundred and ten days, were stepped up to 3 cc. on April 4 and to 4 cc. on May 20. She had by this time become so unusually alert and active she was a constant source of surprise to her relatives, and to keep her occupied she finally was given a position as a messenger girl in the ambulatory clinic.

She had gained in three months, from March 16 to June 28 when finally discharged, from 30.5 to 35.5 Kg., which almost equaled her gain (8 Kg.) during the preceding seven years. It was very difficult to be equally certain about her measured increase in height (from 134 to 135.5 cm.), for she stood more erect and variations of a centimeter or two occurred from day to day.

This, then, may be taken as a representative picture of dual hypopituitarism involving both factors of sex and growth; and the slow accession of growth the child has shown is ascribable to what remnants of the normal gland, relieved of pressure, have retained some degree of activity. Certainly the preparation of growth hormone, either from insufficient dosage, from too long delay in its administration or too short a time given to it, has shown no appreciable effects on the plotted graph

* Her blood studies, taken on March 8, had shown a nonprotein nitrogen of 15.07 mg. per hundred cubic centimeters, with a urine elimination for the twenty-four hours of 2.98 Gm. Corresponding studies made after the injections had been started showed a blood nonprotein nitrogen of 32.08 mg. per hundred cubic centimeters and a urine elimination of 5.56 Gm.

(cf. fig. 10). And though there was an acceleration of weight and a definite improvement in the child's general condition, her weight (cf. fig. 11) quickly dropped off on cessation of the treatment, in full conformity with what happens to laboratory animals when the daily administration of the growth hormone is interrupted.

The preparation of anterior lobe pituitary preparation which was employed was markedly potent when tested on a dwarf rat, whose weight had remained unchanged for more than a year after hypophysectomy. It, however, is obviously far from the ideal product necessary for effective substitutional therapy. Engelbach has recently (1932) reported [45] the case of a female pituitary dwarf 9 years of age who received over a period of eight and a half months subcutaneous injections of 9 cc. of a purified Evans growth hormone, during which period an increment of 2 7/10 inches (6.75 cm.) in height and a gain of 7½ pounds (3.45 Kg.) in weight were recorded.

Reichert failed to observe [105] (1928) any effect on the growth of a puppy to which from the seventh to the eleventh month after hypophysectomy daily subcutaneous injections of the minced pituitary gland of a rabbit had been given. The only response was an imperfect sexual maturation with continued estrus; the failure to stimulate growth was ascribed to probable closure of the epiphyses. I, however, am informed by Dr. Evans that by the injection of 25 to 40 cc. daily of the more highly purified growth hormone he has recently described,[49] which is essentially free from the sex principle, it has been possible to bring about normal growth without acromegalic manifestations in a puppy hypophysectomized [106] by Dr. Reichert at eight weeks, treatment having been begun four weeks later.

While we may any day expect revelations in regard to this important matter of substitution therapy for dual hypopituitarism, the large amounts of the most effective known extract that must be intraperitoneally injected day after day effectively to compensate for the deficiency in experimental canine hypophysectomy precludes its clinical use; and the daily implantation of glands taken from the same species, so effective in dwarfed rats,[114] is unfortunately inapplicable to human beings.

Growth and Sex.—Why should Nature have given to the pituitary body the control of two such important but, so far as can be seen, wholly unrelated activities as that pertaining to growth and that essential to reproduction, which more appropriately might have been controlled from a more caudal station? One would assume that they must somehow work together, for very similar nervous impulses must act on them, and the fact that adolescence normally occurs during a period of very rapid growth would suggest that they at least do not work in opposition as some of the early experiments with the injection of growth extracts had suggested.[52] The therapeutic problem of the dwarfed child whose case has just been cited would have been simplified had the deprivation syndrome not been dual but consequent on the loss of either hormone by itself.

For want of any known agent capable of destroying or inactivating one type of secretory cell while the other is left intact, the possibility of studying by experiment the deprivation effects of either element singly is precluded. That such conditions, however, at least so far as the acidophils are concerned, may occur spontaneously has been shown by Smith and MacDowell,[117, 118] who have made the surprising discovery that a defective gene has led to a congenital absence of acidophilic elements in the hypophysis of the hereditarily dwarfed mice of the Dunn strain. In these animals the growth principle alone is suppressed, leaving the gonadotropic hormone essentially unaffected else there could be no continuance of the species. Should it prove that all the elements of the adenohypophysis of these dwarfed mice possess a Golgi apparatus invariably of basophilic type, while that carrying the factor of growth to the acidophilic cells is lost, it will be of even greater interest from the standpoint of genetics. But even as they stand, these important observations indicate that the hormones of growth and sex have a separable rather than interdependent action.

Growth in the abstract is a highly mysterious process. It can unquestionably be checked by pituitary insufficiency, however brought about, or stimulated by administering the appropriate pituitary hormone. At the same time, it is well known that an inadequate diet and unhygienic surroundings may similarly impede a child's growth just as a change from unfavorable to more favorable surroundings where sunshine, fresh air and better food are plentiful may stimulate it. What if anything has the pituitary body to do with this? My friend, Dr. L. B. Mendel, a few years ago informed me that by an improved diet alone he could produce rats as large as those given pituitary injections, and suggested that the question be put to the test.

Accordingly, Drs. Bryan and Gaiser,[24] basing their study on the number of days required for 60 Gm. rats to attain a weight of 200 Gm., found that those on an ordinary diet for control purposes required an average of 50 days; those on Mendel's special growth diet required an average of 38 days; those on an ordinary diet supplemented by growth hormone required an average of 37 days; while those on Mendel's special diet supplemented by hormone injections required an average of only 28 days—a growth rate of 6 to 7 Gm. *per diem* which they regarded as the maximum attainable.

Polyphagia, as is well known, is a symptom of acromegaly; and dogs when injected with growth hormone become ravenous eaters. So, in the attempt to interpret these experiments, the question immediately arose as to whether the injections merely served to increase appetite or whether they actually stimulated growth by somehow making the nutriment more available as a building material.

We subsequently learned from Dr. Mendel that his co-workers, Anderson and Smith, had prepared a still more effective diet through which in the rat an average daily growth of 7.3 Gm. might be attained. And feeling that Dr. Mendel was not as yet convinced of the efficacy of the growth-promoting hormone by itself, we determined to see whether diet alone could effect the size of totally hypophysectomized rats whose weights never excede that of the preoperative level. It was

found that the improved diet had no influence in starting growth. However, so soon as the administration of the growth hormone was begun, the animals promptly began to gain weight with a rapidity proportionate to the excellence of the different diets employed. On the other hand, cessation of the daily injections of the hormone was promptly followed by a loss of weight irrespective of the quality of the diet.

These experiments appeared to us to show the superiority of the hormone to diet as a growth-promoting influence, though they have left the question of appetite unanswered, for they were complicated and difficult enough to carry through without attempting to determine the precise number of calories the more rapidly growing rats consumed in comparison with those which grew more slowly.

It has been customary, as we have just seen, to measure the growth of four-footed laboratory animals in terms of weight, and the published graphs [53] consequently are difficult to transfer to the clinic with its plantigrade subjects whose measured erect height is the basis of registration. The closest parallel we have to what experimental gigantism in lower animals might be like if produced by a chemically pure hormone of growth is the exaggerated height occasionally attained by young persons in the period before epiphysial closure normally occurs. While it is not easy to determine just where overgrowth of this kind ceases to be merely excessive and becomes pathologic, I may cite two examples of patients at the present time under observation—both of them young normally adolescent lads, of whose rapid increase in stature records have fortunately been kept over a period of five to six years.

THE CASE OF JOHN J. This boy, now 16½ years of age, was born July 17, 1916, weighing 7½ pounds. As a child he was always considered to be somewhat undersized, but suddenly at the age of 8 he began to grow with unusual speed. Precise records unfortunately were not kept until two years later, but in the five years between March 26, 1927 (10 years, 8 months) and Jan. 2, 1932 (15 years, 6 months), he grew 36 cm. at the almost constant rate of something over 3 inches (7 cm.) a year.

When he first came under observation in September, 1931, he was found to be a normally proportioned, adolescent youth 6 feet, 4¾ inches (192 cm.) tall, and with a span 7 cm. greater than his height. His weight was 202 pounds (91.8 Kg.). Roentgenograms of the skull showed large accessory sinuses (fig. 8) and a suspiciously large sella which measured 14 by 17 cm. The long bones were normal in appearance with open epiphyses. His basal metabolic rate was normal. His blood pressure was 110/70.

No treatment was recommended, and the boy's parents were encouraged to look on the condition as indicating nothing abnormal. However, three months later, in January, 1932, he was brought in again because of the complaint of headaches and eye strain. What was taken to be early evidences of upper bitemporal defects in the visual fields were disclosed, and, fearing that after all he might conceivably have a pathologic hyperplasia of acidophilic elements, the pituitary gland was irradiated. During the next three months there was no measurable increment of growth when it again began to move up, and in July, 1932, the gland was again subjected to irradiation.

Fig. 8.—The slightly enlarged pituitary fossa in the case of John J. (natural size).

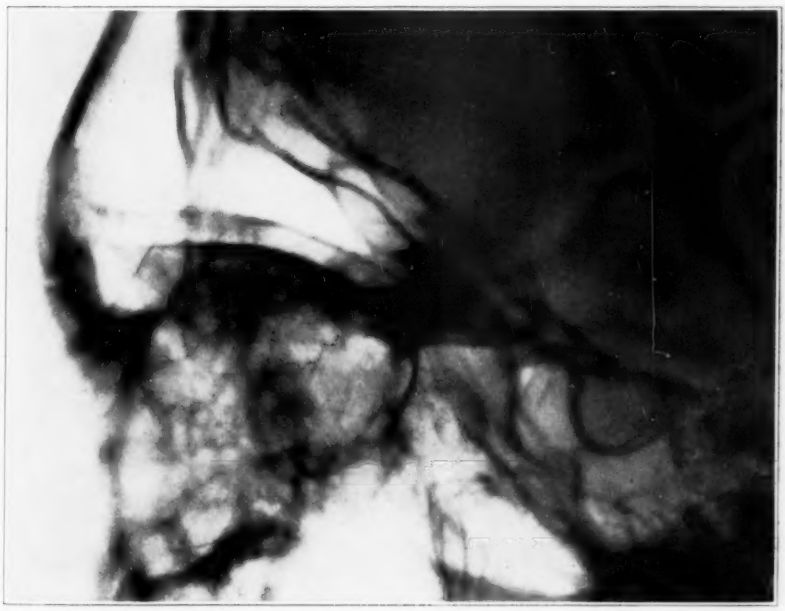


Fig. 9.—The small (for size of skull) pituitary fossa and large sinusoidal spaces in the case of Charles D. (natural size).

In the twelve months which have elapsed since the first of these radiotherapeutic sessions, there has been a growth of only five eighths of an inch instead of the yearly increment of 3 inches which his carefully plotted curve of growth would have led one to expect.

THE CASE OF CHARLES D. This boy, an orphan, born May 20, 1917, had been a frail and undersized child with a congenital dislocation of the lens in each eye, fortunately correctable by glasses. At the age of 7, he suddenly began to grow with great rapidity and when first seen, Oct. 17, 1927, at 10½ years of age, he was said to have grown 4 inches in the preceding twelve months and to have gained 60 pounds (27.2 Kg.) in weight.

He presented a not unfamiliar endocrinologic problem suggestive of adiposogenital dystrophy combined with overgrowth. Roentgenologic studies showed a disproportionately small sella (fig. 9), large accessory nasal sinuses, an area of calcification in the region of the pineal gland and normally open epiphyses. No treatment was recommended, and his guardians were advised to let him work out his own salvation. That he was genetically entitled to be tall was indicated by a family history of tall forebears on both sides of his family and by his having an elder brother who measured 6 feet, 2 inches in height and weighed 250 pounds.

Five years elapsed, when on Oct. 20, 1932, he again came under observation. He was then 15½ years of age, had passed through a normal adolescence, had lost his adiposity and become a spindling youth 6 feet, 7½ inches (201.8 cm.) tall. A careful record of his height and weight had fortunately been kept by his family physician, Dr. R. J. Carpenter, who during 1929 had found the boy to have glycosuria and low blood pressure (98/70), but these symptoms had spontaneously disappeared.

To see whether the excessive growth might be checked, as it appeared to have been in the preceding case, the hypophysis was irradiated under Dr. Sosman's direction six months ago. Since then, there has been no measurable increment in stature—a short time, to be sure.

On the accompanying graph (fig. 10), the growth of these lads has been carefully plotted with precise attention to the detail of the month of age at which the recorded measurements were taken, and the curve is a surprisingly regular one. It can be seen that their stature far exceeds the extreme upper limits of accepted heights for males of their age.* The x-ray treatments were given partly on the grounds that radiation is known to have a definitely inactivating effect on the growth-promoting adenoma of acromegaly, and partly because the prolonged x-ray treatment of a brain tumor of a young girl had inhibited her growth when compared with that of her identical twin sister. Whether the knuckle and plateau shown in the growth curve of these boys was caused by, or fortuitously coincided with, the radiation remains uncertain for want of such a control as would be deemed necessary in laboratory experimentation. The weight of John J. has not been taken

* The normal average height for males and females with the upper limit for males and lower limit for females in the shaded areas of the chart are plotted from Professor Bardeen's detailed figures recently prepared for the Child Conference in Washington.

with the same regularity as his height, but he had always been a normally proportioned youth with a proper height-weight ratio. Charles D., on the other hand, whose weight and height have always been taken together, has shown (cf. fig. 11) extraordinary fluctuations in weight as taken by different observers even though his progressive increment of height meanwhile remained unaffected.

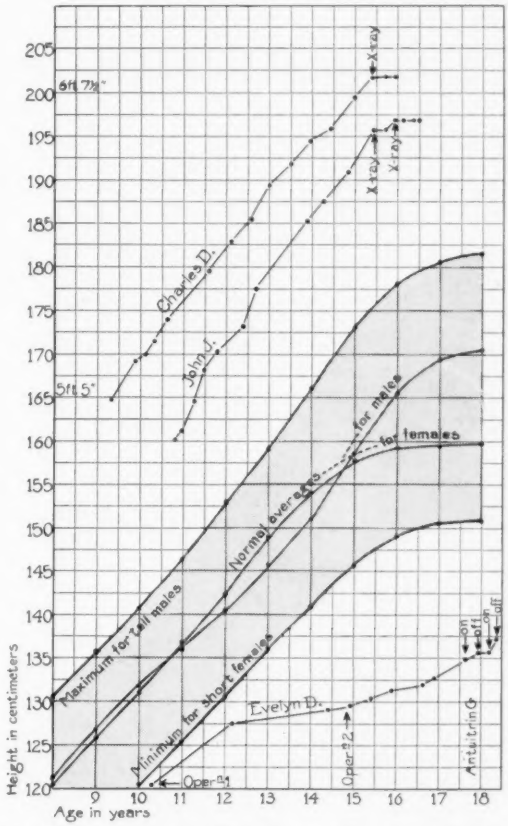


Fig. 10.—Height-age curves of Charles D., John J. and Evelyn D., compared with normal averages in shaded areas.

What, in terms of pituitary function, can be said of these overgrown 15 year old, normally adolescent boys? Are hereditary influences involved? Is their unusual height ascribable to a growth-stimulating diet with present-day attention to vitamins, or to an overactive pituitary gland, or possibly to the two in combination?

While precise figures are difficult to get at and properly to appraise when secured, it is a matter of common observation in recent years that children tend to be taller than their parents. Recalling that when I was a college undergraduate an anthropologically minded gymnasium director had annually made detailed measurements of all students—a custom which has since been continued—I have from this source obtained the comparative figures relating to the single factors of age and height of the present freshman class and that of forty years ago. Similar

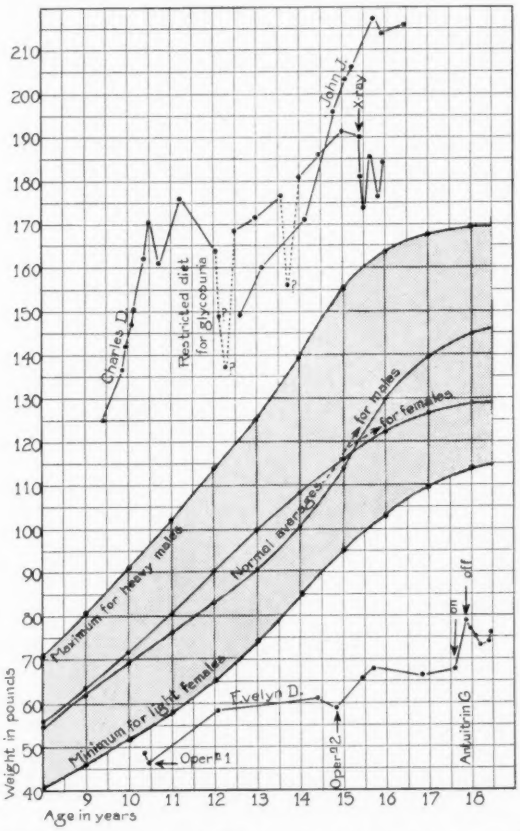


Fig. 11.—Weight-age curves of Charles D., John J. and Evelyn D., compared with normal averages in shaded areas.

figures have also been obtained from two other New England colleges. As it turns out, the average age (viz., 19½) of freshmen in 1892 was a year older than that (viz., 18½) of the freshmen in 1932, from which, all other things being equal, those of forty years ago should more nearly have attained their full stature.

The combined figures of the three institutions, however, show that only 5.67 per cent of the freshmen in 1892, in contrast to 19.47 per cent of the present, 1932, freshmen, were 6 feet or over. In other words, forty years ago *circa* one out of

every twenty matriculating students was 6 feet or over (the tallest 6 feet, 4 inches) whereas today *circa* one out of every five (the tallest 6 feet, 7 inches) is 6 feet or over.

2. THE ACIDOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

Let us now turn to the consideration of pathologic overgrowth as represented in gigantism and acromegaly. Both conditions are now known to be associated with an adenoma the preponderance of whose elements in the active stage of the disorder show acidophilic granules.[12] This fact has provided the most dependable evidence at hand that the growth hormone actually is a product of these cells; and it is now made more certain by the recent disclosure I have mentioned [117] regarding the absence of acidophilic elements in the pituitary glands of hereditarily dwarfed mice.

But if clinical gigantism and acromegaly are an unadulterated expression of overactive acidophilic elements resulting in an excess of growth hormone alone, why should these states so often be accompanied by dystrophic changes in the reproductive apparatus? It will be recalled that Evans' giant rats, and the acromegalic dogs produced in my laboratory, became not only overgrown but sexually dystrophic in the course of the experiment; but in neither laboratory was there then available a growth extract uncontaminated by the sex-maturing principle. And so far as the clinical disorders of like kind are concerned, reference has already been made to the fact that a growing adenoma composed of one type of cell may in time through compression destroy the functional activity of the remaining normal elements in the gland.[65]

So for want of a simon-pure growth hormone, it is impossible to say with certainty whether excessive growth can be experimentally produced without associated gonadal effects. Nevertheless, what clinical evidence we have points in that direction. It is strongly suggested by the fact that in many acromegalics the evidences of sexual dysfunction are long delayed; and when the adenoma is too small really to expand the sella, there may, for example, in affected women be no interruption whatsoever of the normal menstrual cycle. Child-bearing, however, is apt to have a pronounced effect in activating the malady—an effect conceivably brought about by the increase of the growth hormone required for the needs of the child and acting at the same time deleteriously on the mother. In this connection, attention may be again called to the suspicion that the Erdheim-Stumme "pregnancy cells" are enlarged chromophobe elements arrested in the course of becoming fullblown granular acidophilic cells of usual type.

In the clinic we must take into account other factors than height and body weight when considering pathologic overgrowth. The acromegalic's stature may even become shorter owing to the immobility of

his thickening vertebrae, while at the same time he disproportionately gains weight. This in part is due to an increasing heaviness and solidity of the bones, in part to the peculiar "edema" of the connective tissues, but more particularly to the disproportionate increase in the size of the visceral organs.

To this feature of the disease—the splanchnomegaly—special attention was drawn in a report with L. M. Davidoff on the postmortem findings in four cases.[40] While it is not so apparent in experimentally induced overgrowth in the rat, splanchnomegaly in the dog after the prolonged administration of growth extracts may be extreme. Whereas the weight of one of our injected animals at the expiration of eighteen months was almost double that of the litter-mate control, the liver of the former was approximately three and one half times as large—an increment far greater than could be explained by the fatty infiltration and passive congestion that was present.

To what can this hypertrophy be ascribed? To an increase in the size of the cells or in their number within a given hepatic unit; or are the number of hepatic units actually increased? Or again, is the enlargement merely due to that sort of connective tissue thickening or edema which causes the puffiness of the cutaneous and subcutaneous tissues? To these questions there is as yet no wholly satisfactory answer.

It would be of little avail to include here the report of a typical case of acromegaly for its features are well known. It, however, is far from being a disorder which affects all its victims in the same way or in equal degree. The following case, which at the present writing is a source of anxiety, may serve as well as any other to show how complicated may be the syndrome and how great may be the difficulties of interpreting the secretory aspects of acidophilic hyperpituitarism in terms of experimental overgrowth in animals, particularly when they become masked and overlain by pressure involvement of the interbrain.

THE CASE OF MRS. E. L. *Postpartum amenorrhea. Continued lactation. Fugitive acromegaly. Enlarged sella with neighborhood symptoms demanding operation. Chromophil adenoma. Subsequent pressure symptoms improved by irradiation. Ultimate symptomatic involvement of hypothalamus from intracranial expansion of tumor.*

Elizabeth L., born in 1893, with an excellent heredity and good general health, married a government official in 1917 when 24 years of age and went to Shanghai to live. She passed through her first pregnancy in 1919 without mishap. A second child, born a year and a half later (November, 1920), was similarly breast fed, but when weaned, at the expiration of twelve months, lactation continued in spite of all efforts to check it. Meanwhile, in the fourth month postpartum (March, 1921), normal menstruation had been resumed and continued for twelve months, when it ceased permanently.

In spite of the continued amenorrhea and persistent lactation, she regarded herself as well until November, 1925, when she began to have severe headaches with blurring of vision; and soon the sight in her right eye became seriously impaired.

Roentgenograms at this time disclosed an enlarged sella. At this juncture (December, 1925) a gynecologist explored the pelvis and, finding the ovaries in "a state of senile atrophy," split them sagittally and implanted under the peritoneum the supposedly normal ovaries from another patient.

On the patient's return to America for a visit the next year (1926), her parents were dismayed at her acromegalic appearance. She was still lactating profusely and troubled by excessive sweating. Not only had she gained some 40 pounds (18.1 Kg.) in weight, but she was distinctly exophthalmic, and her features had become coarse, hirsute and grossly enlarged with thick nose, lips and tongue. The ophthalmoscope disclosed a primary optic atrophy with definite haziness of the disk margins but no measurable swelling. Bitemporal field defects indicated

Fig. 12.—The ballooned sella in the case of "fugitive" acromegaly with prolonged lactation (natural size).

involvement of the chiasm by tumor; visual acuity in the right was reduced to appreciation of finger movements. Roentgenograms showed the phalangeal tufting characteristic of acromegaly and an expanded sella (fig. 12). The metabolism was —2; blood pressure, 110/65; height, 166 cm.; weight, 78.5 Kg.

To preserve vision, a transphenoidal operation (this being the procedure favored at the time) was performed (August, 1926), and as much as possible of the soft intrasellar growth was removed. The tissue showed cells of acidophilic type with alpha granules (Bailey) scattered among large chromophobe elements. From this operation the patient made a good recovery, with temporary cessation of headaches and improvement in vision. Active lactation, however, persisted, and she continued to gain weight, which by November reached 194 pounds (88 Kg.).

She reentered the hospital in February, 1927, because of a return of severe headache with occasional attacks of dizziness and projectile vomiting. Lactation and excessive sweating still persisted, and she at times was unduly somnolent. There was an unmistakable low grade of papilledema, particularly marked on the left. Her teeth which had become greatly decayed were extracted at this time at her insistence, and the pituitary region was thoroughly irradiated. This was followed by prompt subjective improvement and disappearance of the headache. There was a gradual diminution of lactation, which by November, 1927, had practically ceased; and though she had continued to gain weight up to 200 pounds (90.7 Kg.), her acromegalic appearance had noticeably lessened.

In February, 1928, her health was so greatly improved that she returned to Shanghai, and for the next eighteen months felt exceptionally well, though the amenorrhea persisted. In June, 1929, and again in September, 1929, she had a convulsive seizure with unconsciousness and incontinence of urine. In March, 1930, she began having peculiar momentary petit mal seizures with a "rush of blood to the head" and uncontrollable evacuation of the bladder. Apart from finding herself wet, the patient had no knowledge of these attacks and showed a curious disregard of them. Severe headaches from which she had been free for nearly three years again appeared with failing sight and hypersomnia. She was annoyed by a bruit synchronous with the pulse, which could be stopped by pressure on the neck. A series of x-ray treatments was given, and she was sent back to America, but before her arrival all these symptoms had disappeared, and there had been a marked improvement in vision.

On her readmission to the hospital (April, 1930) she was in good spirits, looked well and was symptom-free. Apart from haziness of the margins of the somewhat pale disks with measurable swelling of one diopter, the examination revealed nothing noteworthy. In June, 1930, she was given further roentgenotherapeutic treatments, and two months later she rejoined her husband in China. There for the next year and more she led an active life and felt reasonably well in spite of occasional petit mal seizures described as trances in which she would void involuntarily.

By January, 1932, the seizures began to grow more numerous and severe and in August, 1932, she returned again to America. On readmission to the hospital for study, she appeared in better general condition than at any previous time. Though still heavy (198 pounds [89.8 Kg.]), her acromegalic appearance was scarcely noticeable. The papilledema had disappeared; the visual fields were wide; visual acuity had improved. The blood pressure was 108/72; metabolism, —11 per cent; there was no polydypsia or polyuria.

The peculiar attacks appeared to come in waves with intermissions of two or three weeks. They were characterized by a bright flush of face and neck with a profuse sweat and involuntary evacuation of the bladder. They so strongly suggested the autonomic (parasympathetic) stimulation brought about by hypothalamic irritation[37] it was finally decided to take ventriculograms. These were finally made (December, 1932) and showed a marked hydrocephalus with a filling defect of the third ventricle.

At this point, the story of the patient begins to get beyond the bounds of the present discourse. The prior history briefly summarized is that of a woman with mild acromegaly coming on after parturition with prolonged lactation, persistent amenorrhea and early evidences of intracranial pressure long unaccounted for and due, as finally shown,

to the suprasellar projection of an acidophilic adenoma into the third ventricle with resultant hydrocephalus and hypothalamic (autonomic) fits.

Fully to unravel the symptomatic effects of this lesion, while possible, is unnecessary here. There are, however, a few points to which special attention may be called:

1. The acromegalic symptoms of overgrowth shown by the patient were "fugitive" [11] and the adenoma, while acidophilic in type, was composed chiefly of large, undifferentiated chromophobe elements. It is not inconceivable that it may have been an adenoma arising from the "pregnancy cells" which, as already stated, may be chromophobe elements arrested in the process of ripening into acidophils. The human pituitary body of pregnancy, when transplanted into immature mice, has been shown by Philipp [95] to have temporarily lost its sex-maturing capacity, which would seem to indicate that the sex-maturing substances in the urine of pregnant women and in the placenta must come from some other source.

2. Whether the cells of the patient's tumor secreted a lactogenic hormone corresponding to the "prolactin" of Riddle [109] could only have been determined by testing the effect, on the previously sensitized mammary glands of animals, of implanted tissue taken from the growth. Both Riddle [110] and Evans [53] feel assured that the adenohypophysis provides such a hormone definitely separable from the principles influencing growth and sex. If that is so, it was probably present (together with other impurities) in the early preparations of the growth hormone, for Putnam's acromegalic dogs showed hypertrophic, lactating mammae.* Conversely, Collip and his co-workers [28] have just shown that hypophysectomy of a rat after parturition leads to a prompt retrogression of the mammary glands with cessation of lactation.

3. In view of what is to follow in describing pituitary basophilism, it will be noted that the patient's blood pressure was invariably subnormal, which may in this case, as in chromophobe tumors, be ascribed to pressure obliteration of the neurohypophysis; and, similarly, her amenorrhea may be attributed to the compression effect of the large tumor on the cells (whatever they may be) that elaborate the luteinizing principle. The skin was pale, coarse, moist and without striae, and the adiposity was generally distributed and not confined to trunk and face.

4. The patient's periods of somnolence as well as the adiposity might conceivably be looked on as of hypothalamic origin, but both are frequently seen in cases of pituitary disease which does not involve the interbrain, and they were unassociated with polyuria. The temporary seizures appear to have been stimulatory episodes comparable to those described by Penfield [94] in the case of a patient with a proven third ventricle cyst.

3. BASOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

So far, very little has been said of the hormone of sex other than that the mechanical effects of chromophobe adenomas of childhood produce a dual deficiency that inhibits both growth and maturation.

* This is not to be confused with the long known galactogogue effect of posterior lobe extracts.

For the same reason, the acidophilic adenoma of acromegaly may in time so compress the residual normal elements that sexual dysfunction is superimposed on the primary symptoms of overgrowth. This at least is the most probable explanation.

While evidence that the growth hormone comes from the acidophilic elements now appears to be conclusive, the attribution of the sex principle to the basophils is still under debate. There have been a few highly suggestive observations in its favor. One of them was the Smiths'[120] demonstration (1923) that the central core of the bovine anterior lobe where basophilic cells abound possesses a greater sex-maturing potency than does the rind where acidophils predominate. Another was the identification by Addison[1] of the so-called "castration cells" as basophilic elements. This in turn was followed by Engle's discovery[40] (1929) that the gland of the castrated rat not only shows a multiplication of these elements but acquires increased potency as a sex-maturing agent, as shown by its effects when transplanted into immature mice.

This reciprocal reaction of Engle proves, however, not to be true of all species. Severinghaus[113] has shown, for example, that castration increases the sex-maturing capacity of the guinea-pig's hypophysis without demonstrable increase of the basophils. What is more, in man and some other mammalian forms, it is the acidophils that appear to be increased in castrates. On the other hand, it is said that in the rutting season and in animals (e. g., the marmot[101, 102]) emerging from hibernation, the number of basophilic cells are augmented; but in view of the known species variability and seasonal variation in the number of these elements, observations of this sort are difficult to appraise.

Furthermore, the quota of basophils is said to be greater than normal in certain clinical disorders, such as vascular hypertension and the uremic stage of renal disease, and I am inclined to believe that the same thing will be found true of eclampsia. More recently, Zondek has reported[137] that the pars intermedia, pars nervosa and stalk of the human (but not of the bovine) hypophysis contains a follicle stimulating substance (prolan A) which he ascribes to the inwandering basophilic elements.

Now it has been recently brought to light that a well recognized polyglandular disorder—in the same sense, to be sure, that acromegaly is polyglandular—not infrequently is associated with a pure basophilic adenoma of the anterior pituitary.[38] Were it not that adenomas of this type have been thought to be exceedingly rare and of no pathologic significance, this disclosure would not have seemed so highly peculiar, and the patients with the disorder would continue as in the past to be looked on as the victims, for example, of osteomalacia, of hypertension or of diabetic obesity.

The external evidences of the disorder are unmistakable when once pointed out, and the accompanying photographs will show how rapidly it has developed in the course of a few months in the young girl, Alice D., 15 years of age, to whose case attention has elsewhere been

drawn.[59] The symptomatic features of the malady (not yet verified, to be sure in this particular instance) are subjoined:

There was a precocious adolescence, at 10 years of age, associated with normal menses which continued for three years and abruptly ceased. She acquired a peculiar plethoric appearance with an abnormal growth of hair on brows, lip and chin (fig. 13). She became increasingly abdominous with progressive increase of purplish striae atrophicae (fig. 14).

She has had persistent backache and become round shouldered with the loss of 4 cm. in measured stature, due undoubtedly to the roentgenologically evident decalcification of the vertebrae and an abnormally high calcium elimination. A spontaneous fracture of the pelvic bone, evidently in a tumor, has healed with callus formation.

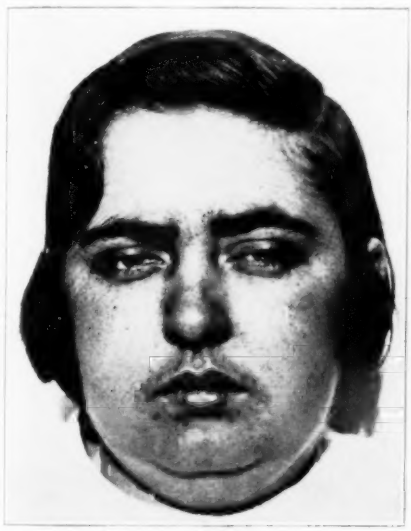


Fig. 13.—Facial hirsuties in a case of pituitary basophilism at 15 years of age.

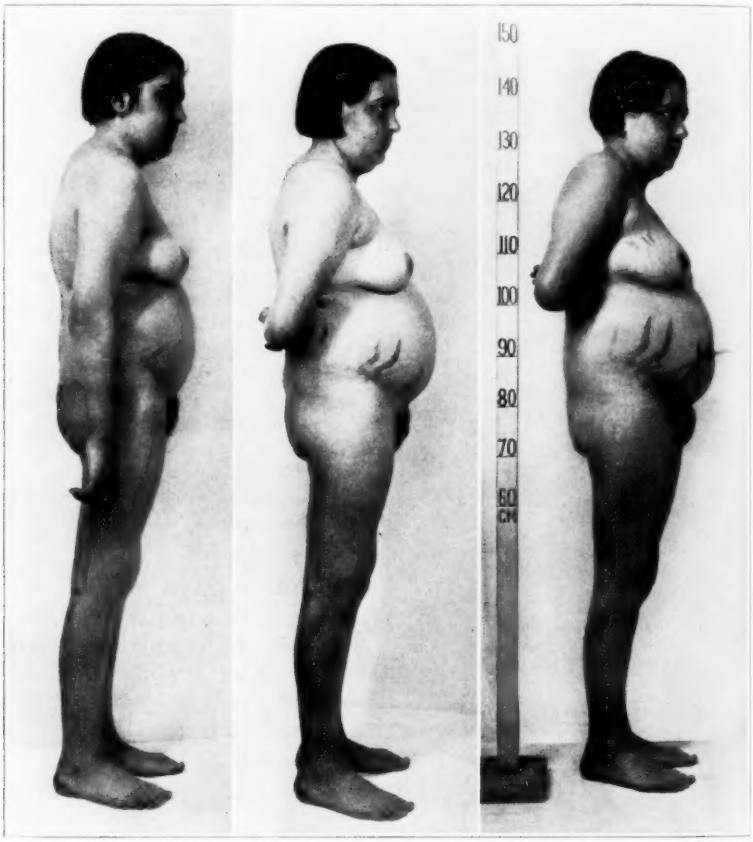
She has a subnormal basal metabolic rate, a lowered tolerance for carbohydrates and a high blood pressure, presumably indicating secondary involvement or imbalance of other glands — parathyroid, thyroid, pancreatic islets and adrenal—to almost any one of which the syndrome might have been ascribed.

Her urine tested by two observers on both rabbits and immature mice proved to contain a follicular-stimulating substance indistinguishable in its effects from prolan A (rho I).*

While from case to case, as is true of acromegaly, the syndrome varies considerably, its frequent association with a basophilic adenoma of the hypophysis must be something more than accidental. The disorder proves to be not uncommon, and suggestive clinical examples are found scattered in the literature dealing primarily with osteomalacia,[59] hypertension,[92] adiposity [100] and dermatologic topics,[66] or merely reported

* In April, 1932, and again in June and August, she was given a series of deep x-ray treatments directed toward the pituitary body. There was an early relief of backache. In August, a definite diminution of the facial hirsutism was noted. By September, her blood pressure, originally averaging 140/105, had dropped to 115/80 and has remained there. In October, the abdominal striae began to lose their bright color. In February, 1933, a normal menstrual period occurred after two years and ten months of amenorrhea with disappearance from the urine of the follicle-stimulating substance.

as an instance of a remarkable disease.[107] In a recent tabulation by Mr. Henderson of the symptoms shown by the patients in our series with hypopituitarism due to chromophobe adenomas (verified or suspected), two of the patients were found to have an elevated blood pressure, and a review of their case histories makes it now obvious



April, 1932 July, 1932 October, 1932

Fig. 14.—Progress of acute pituitary basophilism (unverified) in six months period.

that they were probably victims of basophilism. Indeed, an unmistakable case (that of Theresa L., cf. fig. 15) has come to light while reviewing, for the purposes of this paper, the polyglandular changes found in the seventeen patients that died after operation for what was formerly diagnosed and indexed in the files as a chromophobe adenoma.

Since hyperadrenalism and possibly other endocrine derangements may provoke a somewhat similar syndrome, it is unsafe as yet to pin too much faith on clinical symptoms alone, and only those examples of the disorder in which a postmortem examination has been held are dependable. Records are at hand of seventeen cases that came to autopsy,* in fourteen of which the condition has been shown to be pituitary adenomas. In two of the three negative cases,[153, 99] the

Fig. 15.—Miss L. Facial hirsutism with verified pituitary adenoma (? basophilic) invading cranial chamber.

gland was said to have been normal without further specification; in the third, the Leyton-Turnbull-Bratton case[58] (in regard to which I over-reached myself in predicting[37] that a basophilic adenoma would be found), no lesion has been detected on recent serial sections

* My attention has been called by Professor Günther of Leipzig to another unmistakable case with a proved basophilic adenoma reported by Drs. Theodor Bauer and Hans Wassing (Zur Frage der Adipositas hypophysarea: Basophiles Adenom der Hypophyse, Wien. klin. Wchnschr. **26**:1236-1243, 1913).

of the gland. Of the fourteen cases actually associated with a pituitary adenoma, in three instances it was a large, unclassifiable growth, only fragments of which were examined, whereas in the other eleven it was a small, circumscribed, typically basophilic lesion.

For the purpose of showing the principal symptomatic and pathologic features of the fourteen cases with verified adenomas, the data,

Verified Pituitary Adenomas Causing Syndrome of Basoph

Number	Case	Date of Report	Sex*	Age: Onset	Age: Death	Type of Adenoma Weight of Hypophysis	Principal Symptoms: Abdominal Obesity	Amenorrhea	Hirsutism	Abdominal Striae	Glycosuria	Metabolic Rate (Basal)	Hypertension	Skeletal Changes
1	Schmorl[131]-Molineus[89]	1913	♀	20	48	Large basophil	Yes	Yes	Yes +	....	....	....	....	Fra
2	Anderson's[3]	1915	♀	21	26	Basophil	Yes	Yes	Yes	Yes	....	....	+ 185	Fra
3	Reichmann's[107]	1919	♀	157	36	"Eosinophilic"?	Face only	Yes	Yes	....	....	....	++ 210	Ye
4	Zondek's[139]	1923	♀	19	24	? Small	Yes	Yes	Yes	Yes +	Yes	....	....	Ye
5	Raab[100]-Kraus[73]	1924	♂	?	31	Basophil 93 mg.	Yes	Impotence	None	Yes ++	Yes	....	....	Ye
6	Parkes Weber's[93]	1926	♀	23	28	Basophil	Yes	Yes	....	Yes ++	....	+20	++ 230	
7	Bauer's[14]	1930	♀	24	36	Basophil	Yes	Yes	Yes ++	Yes	Yes	+28	+180	S
8	Wieth-Pedersen's[135]	1931	♂	20	24	?	Yes	Impotence	None	Yes ++	Yes	Normal	+100	
9	Teel's[120]	1931	♀	15	20	Basophil	Yes	?	Yes	....	....	+33	....	
10	Moehlig's[85]	1932	♀	34	43	Basophil	Yes	Castrate	Yes	Yes	....	+21 −1	++ 230	
11	Bishop Close[23]	1932	♀	15	22	Basophil	Yes	Yes	Yes ++	....	Yes	....	++ 250	Fra
12	Berblinger's[22]	1932	♀	?	?	Basophil	None	Castrate	Yes +	Yes	....	....	....	Ye
13	Miss L No. 14627	1921	♀	18	45	Large invasive	Yes	Yes	Yes +	Yes	Yes	−4	+170	
14	Miss P No. 42211	1932	♀	20	33	Basophil 71 mg.	Face chiefly	Yes	Yes ++	Yes ++	Yes	−40 −1	++ 240	Fra

* ♀ indicates female; ♂, male.

so far as the fragmentary protocols which accompany many of the reports permit, have been assembled in the accompanying table.* To a detailed consideration of the last of these cases we may now turn. As will be told, I had seen the patient briefly in consultation twelve

* Attention may be drawn to the number of patients that died from acute pulmonary complications ascribed to edema.

years ago and not again until she was recently referred to the hospital by Dr. Goodale of Boston as having a case of probable pituitary basophilism.

THE CASE OF MISS P. *Onset of amenorrhea with plethoric adiposity, purple striae atrophicae and hypertension at 19 years of age. Relative subsidence of symptoms for ten years followed by exacerbation. Multiple fractures, glycosuria and hyper-*

Principal Symptoms and Ductless-Gland Changes as Recorded

	Postmortem Findings							
Thyroid and Cysts	Parathyroids	Thymus	Pancreas Islets	Hyperplasia Adrenal Cortex	Gonads	Arterio-sclerosis	Osteomalacia	Cause of Death
Colloid goiter	Large adenoma	.....	Fatty	.....	Atrophic	.....	Brown tumors	
Fatty enlarged	"Normal"	Atrophic	.....	Yes	"Senile"	Yes	"Brittle bones"	Asthenia
Small; low thyroidal	.....	Not identified	Normal	Yes 8.5-15 Gm.	Atretic; no corpora	Yes +	?	Following adrenalectomy
Small	.....	Atrophic	Fatty	.....	Follicular atresia	.....	Yes + +	Erysipelas
Fatty enlarged	Large fatty 0.16 Gm.	.....	94 Gm.	?	18.3 Gm.; no spermatozoa	.....	Yes + +	Sepsis
Not "goitrous"	.....	"Chiefly fat"	.....	Yes 11.9 Gm.	Atretic; no corpora	Yes	?	Pulmonary edema
Small; low thyroidal	.....	.....	Normal	None	Follicular; no corpora	Yes	?	Following adrenalectomy
Small	.....	.....	Normal	Yes	.....	.....	.....	Respiratory dyspnea
Fatty enlarged	.....	"Persistent"	Slightly enlarged	Yes	1 corpus luteum	.....	.....	Meningitis
Autopsy restricted to brain					.....	.....	.....	Following thyroidectomy
Low thyroidal	.....	.....	.....	.....	Atretic; no corpora	Yes	.....	Pulmonary edema
	.....	.....	.....	Yes	Castrate	.....	Yes "senile"	?
Small 0.5 Gm.	Large fatty 0.1 Gm.	Not identified	90 Gm. fatty	Yes 9-10 Gm.	Atretic; no corpora	None (?)	.....	Pituitary operation
Small 1 Gm.	Large fatty	Atrophic	Fatty	Yes	Atretic; no corpora	Yes + +	Yes, slight	Pulmonary edema

tension. Death from acute pulmonary complications. Postmortem examination. Basophilic adenoma; hypertrophic adrenal glands; extreme atherosclerosis.

Oct. 24, 1932: Admission of Miss P., 33 years of age.

Past History.—Born of healthy parents with an untainted family history, she, as a child, in addition to frequent "colds," had had measles, mumps, whooping cough, chickenpox and an attack of erysipelas; in 1908, an emergency appendectomy had been performed. She attained a normal adolescence when 13 and grew

into an intelligent, vigorous and ambitious young woman. She entered college at 18, but became unhappy there and withdrew at the end of her second year. This determination she ascribes to restlessness, for she believes herself to have been "nervous, irritable, tense and emotionally unstable as long as she can remember." Because of her round face, she had been nicknamed "moony."

Present Illness.—Her want of success at college may have been due to physical rather than temperamental causes. It at least coincided with the symptomatic onset of her malady, for in June, 1919, she ceased to menstruate, and subsequently while at a summer camp she developed a ravenous appetite. Always unduly fond of sweets, she began rapidly to gain weight, particularly noticeable in the face and abdomen. She became "gross, florid and bloated about the eyes (piggy-eyed)." During the summer she broke her ankle. Purplish striae of the body and arms began to appear at this time, and she has never since ventured to wear a sleeveless dress. In December, 1919, she found herself easily fatigued and acquired a definite polyuria and polydipsia. At the same time she began having headaches with blurred vision, tinnitus, dizziness and numbness of the hands.

Toward the end of February, 1920, because of a sudden fainting attack she came under the care of Dr. E. P. Joslin who found she had a moderate hyperglycemia with glycosuria and a basal metabolic rate of —30 per cent. The puffy appearance of her eyes and face, dry skin, marked supraclavicular fat pads, and her complaint of being mentally sluggish strongly suggested myxedema.

On March 13, 1920, she was first briefly seen in consultation with Dr. Joslin. Her facial hypertrichosis and the peculiar disposition of the adiposity with extraordinarily widespread striae atrophicae associated with a moderate hypertension (140/100) indicated a polyglandular syndrome recognized as resembling that in the case of "Minnie G."[38] No therapeutic suggestions were made.

By January, 1921, she had become increasingly hirsute and "bloated," and at this juncture she came under the care of Dr. Timme at the Neurological Institute in New York. There she was given salt baths, graded exercises and various glandular preparations, including lutein, thyroid and pituitary. After four weeks' treatment, her weight was greatly reduced, the hirsuties had disappeared, and normal menstruation was resumed. From this time for a period of five years, she continued under various combinations of glandular treatment and regarded herself as reasonably well.

In 1926, her face again began to get heavily bearded and after trying various forms of proprietary treatment, she finally resorted to the daily use of a razor. In May, 1927, her adenoids, tonsils and impacted wisdom teeth were removed, and it was noted by the attendant that her blood pressure was high (155/115). In 1929, she had a "nervous breakdown." During March, 1930, she was elaborately studied at the Evans Memorial Hospital. At this time, the urine showed some albumin and occasional hyaline casts with normal phthalein test. She had a low sugar tolerance, a fluctuating hypertension, basal metabolic rate of —14 per cent and a cardiac enlargement. The possibility of hyperthyroidism, virilism, primary ovarian disorder and myxedema was discussed. She was subsequently under observation at the Lahey Clinic as presenting a possible thyroid problem.

In January, 1931, the menstrual periods, after having been essentially regular for ten years, again ceased. In July, 1931, she was found to have a marked hypertension, from 220 to 250 systolic. She nevertheless passed the summer of this year with Grenfell in Labrador and enjoyed her work there.

In April, 1932, she fell and broke her humerus. During the following summer she became conscious of a change in disposition. She began to complain of polydipsia, occipital headaches, palpitation, shortness of breath, and swelling of feet and ankles. The fatness of face and shoulders, dryness and pigmentation of the skin,

cyanosis of dependent hands and feet had markedly increased. She observed that large ecchymoses would follow the slightest bruise and that a cut or scratch would bleed excessively. At this juncture, in October, 1932, she was referred to the Brigham Hospital for study.

Physical Examination.—The patient was a rather tall woman, 5 feet, 9½ inches (175.8 cm.), weighing 63.5 Kg., with a peculiar moon-shaped, recently shaven face and clipped eyebrows. The eyes were puffy; there were posterior cervical and supraclavicular fat pads. She was not appreciably round shouldered other than

Fig. 16.—Striae atrophicae of arm, axilla and breast.

the cervical fat pad would account for. Though not particularly abdominous, the parietes were somewhat pendulous and flabby. The extremities did not participate in the adiposity. Over arms, axillae, breasts, abdomen, hips, groins and thighs were an extraordinary number of broad, pale striae atrophicae which deepened in color on slight rubbing (fig. 16). The lower extremities showed marked pigmentation and scarring of the dry and scaly skin with several large fading ecchymoses from recent trivial contusions.

The blood pressure averaged 220/170; the urine showed a trace of sugar and of albumin with no renal elements. There was a variable polyuria amounting to *circa* 3 liters. The basal metabolic rate was —10 per cent. The detailed blood exami-

nation showed 4,720,000 erythrocytes with hemoglobin (Sahli) of 106 per cent = 14.63 Gm. The nonprotein nitrogen was 46.97 mg. per cent and the cholesterol 192.3 mg. per cent; all other chemical tests being within normal limits.

Roentgenograms showed (Dr. M. C. Sosman) "a slight diffuse atrophy of the vertebral bodies without collapse or deformity; normal detail of the cranial bones; a sella of normal dimensions (fig. 17) but hazy outline. Multiple small tiny shadows in both flanks suggesting renal calculi—a common finding in hyperparathyroidism."

The patient was transferred to the Huntington Hospital where, through the kindness of Dr. J. C. Aub, her elimination was thoroughly studied. He reported essentially normal blood content for calcium phosphorus and phosphotase and a

Fig. 17.—Sella of normal configuration but hazy outline from decalcification in case of Miss P.

normal elimination of both calcium and phosphorus. She showed a low sugar tolerance and a high nitrogen output,* as shown by an average loss of 6.7 Gm. daily on a balanced diet containing 56 Gm. of protein.†

* This condition of "azoturia" (Woodyatt) was also observed in another example of the disease (case 11) in a former report.[38] In acromegaly, on the contrary, there appears to be a prompt ultilization of nonprotein nitrogen.[128]

† Biologic tests of the patient's urine at this time were made by Dr. Fuller Albright who found on tests with rats no follicular-stimulating substance (rho I) such as had been found in the urine of Alice D. when tested on rabbits. This effect would normally be expected on the basis of Zondek's[136] explanation of amenorrhea as conditioned by the overproduction of the follicularizing hormone.

On her readmission to the Brigham Hospital, the pituitary body was irradiated on four successive days without immediate effects of any appreciable kind. She was discharged Nov. 12, 1932. She returned to her home and resumed her usual activities. On the night of December 3, she had been to the theater, and though complaining of fatigue, she nevertheless joined a supper party and retired about midnight. An hour later, she awoke with dyspnea, became increasingly cyanosed, and died twelve hours later from what what was supposed to be acute pulmonary edema.

Autopsy (Drs. R. Z. Schulz, George Hass and author).—Forty-eight hours had elapsed before news of her death was received and an autopsy could be solicited and performed. The body had fortunately been well embalmed. The general condition, in brief, showed marked adiposity, particularly abdominal and mediastinal. There was no splanchnomegaly or apparent anomaly of the liver (1,740 Gm.), spleen

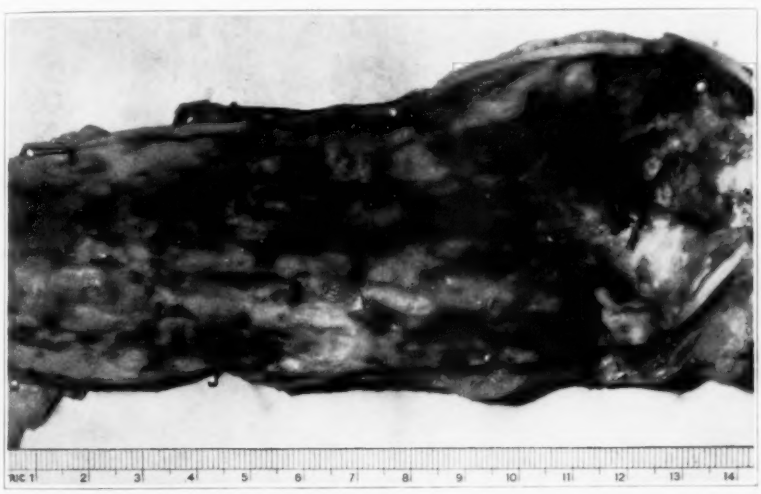


Fig. 18.—Marked atherosclerosis of aorta (natural size).

(100 Gm.) or pancreas (65 Gm.). The kidneys (170 and 175 Gm.) had slightly adherent capsules, and on section numerous minute brownish calculi were visible in the calices of the pelves. The heart was enlarged (695 Gm.), and the lungs (720 and 620 Gm.) showed merely a few patches of congestion. There was an advanced degree of atherosclerosis chiefly apparent in the aorta and larger arteries. The bones, particularly the vertebral bodies, were easily cut with a knife, suggesting osteoporosis, but the tissue showed no gross change.

The histologic study of these organs and tissues principally showed: (1) a chronic vascular nephritis, with sclerosed glomeruli and calcific deposits; (2) hypertrophy of the cardiac musculature; (3) apart from the arterial changes, an essentially normal structure of spleen, liver and pancreas; (4) an acute bronchitis and bronchopneumonia. The bones showed definite osteomalacia. The Paneth cells of the intestine were noted as being particularly prominent. A section of one of the cutaneous striae showed obliteration of the papillae of the corium with swollen and fragmented elastic fibrils. There was marked atheromatous degeneration of the aorta (fig. 18) and large arteries.

The Endocrine Organs.—The *adrenal glands* (fig. 19) were hypertrophic; the left (14 Gm.) measured 8 by 3 cm.; the right (12 Gm.) measured 7 by 4 cm. and showed possible small adenomas on fresh section. A small nodule of adrenal tissue was identified in the stalk of the ovary. The heavy yellow cortical layer of each gland measured 2 mm. in thickness. The evident hyperplasia was found histologically to be restricted to the zona fasciculata (cf. fig. 31) whose cells were distended with lipoid material.

No *thymic tissue* could be definitely identified in the mass of mediastinal fat, but an area of suspicious tissue was removed for study. Sections show only a few atrophic epithelial cords of thymic tissue, no Hassall's corpuscles being found.

Fig. 19.—Cleanly dissected adrenal glands: left, 14 Gm.; right, 12 Gm. (natural size). (Cf. fig. 31.)

The *thyroid gland* (fig. 20) was small (15.1 Gm.). The parenchyma was composed of closely packed, rather small acini containing deeply-staining colloid. There were no papillary infoldings and the cells were of a low cuboidal type.

Four *parathyroid glandules* were identified, two of them slightly enlarged, measuring, respectively, 7 by 5 by 2 and 10 by 5 by 3 mm. in diameter. Histologic study of the larger of them showed an essentially normal appearance apart from the fact that approximately two thirds of the volume of the gland was composed of fat. The cells are of the pale variety with a few scattered acidophilic elements and occasional droplets of colloid.

The *pancreatic islets* are numerous and appear to be normal in their structure.

The *uterus, tubes and ovaries* together (fig. 21) weighed 65 Gm. The uterus was small, acutely retroflexed, and the endometrial as well as the cervical glands

Fig. 20.—The 15 Gm. thyroid gland (natural size) with adherent parathyroids.

Fig. 21.—Uterus, tubes and ovaries (slightly reduced); weight, 65 Gm.

were found to be uniformly atrophic. The right ovary measured 40 by 25 by 20 mm. and contained a superficially placed thin-walled cyst measuring approximately 25 mm. in diameter. The left ovary measured 30 by 12 by 15 mm. and showed no superficial cysts, but on fresh section numerous small cystic areas were apparent. Microscopically, the ovaries are found to have an essentially normal stroma in which a few large corpora albicantia and numerous follicular cysts of variable size are embedded (cf. figs. 33 and 34). The germinal epithelium is tall and columnar in type and does not appear to be abnormal; numerous primordial ova are to be seen. The cystic follicles are lined by atretic granulosa cells showing mitoses, in some of them a cumulus containing an atretic oocyte being discernible. The theca interna is well vascularized, cellular, both mitotic and pseudomitotic figures being numerous.

The Pituitary Body.—Since it is with the hypophysis in this case that we are chiefly concerned, it deserves more detailed consideration. When the brain had been removed leaving the sella exposed, the diaphragma was found to be defective leaving exposed the larger portion of the upper surface of a nonprotruding hypophysis with its attached stalk. On carefully removing the gland (fig. 22), it proved to be small (71 mg.) and of normal appearance. Scarcely hoping to find the predicted lesion, the organ after fixation was serially cut in coronal sections. Three of these sections are shown in low magnification in the accompanying photomicrographs (fig. 23 *A*, *B* and *C*). The first of them (*A*) passes through the largest diameter of a lateral and anteriorly situated oval adenoma of pure basophilic type (cf. figs. 24 and 25) measuring 7 by 2.5 mm.

Fig. 22.—Upper surface of pituitary body (natural size); weight, 74 mg.

The second section (fig. 23*B*) through the center of the gland transsects the anterior part of the neurohypophysis and shows the marked invasion of the lobe by inwandering basophilic elements (cf. fig. 26). These invading cells, either by a holocrine or apocrine method of secretion, appear to disgorge their granular cytoplasm, masses of which are not only to be seen in the vicinity of the more deeply invading cells (fig. 27) but can be traced into the loose tissue of stalk and tuber from which region, however, the soluble substance has largely been dissolved out (?) in process of fixation of the tissues.

The third section (fig. 23*C*) transsects both neurohypophysis and stalk and shows (to the right side) a part of the anterior lobe in which acidophilic and basophilic elements are present in normal proportions. In this section only a small crescent of the highly vascularized tuberal cuff of the adenohypophysis remains apparent on the anterior (upper) surface of the transsected stalk, whereas in figure 23*B* it completely surrounds the stalk. Due possibly to the patient's extreme cyanosis at the time of death, the "portal system" (Popa and Fielding;[97] Basir[13]) of diencephalo-hypophysial veins which passed through the stalk was greatly engorged (fig. 28). On high power magnification, some of the communicating vessels of this system prove to be filled, almost to the exclusion of erythrocytes, with what appears to be granular secretion (fig. 29). Clumps of the same appearing substance are to be seen here and there in the loose meshed glia of the neurohypophysis and can be traced even into the stalk and region of the tuberal nuclei.

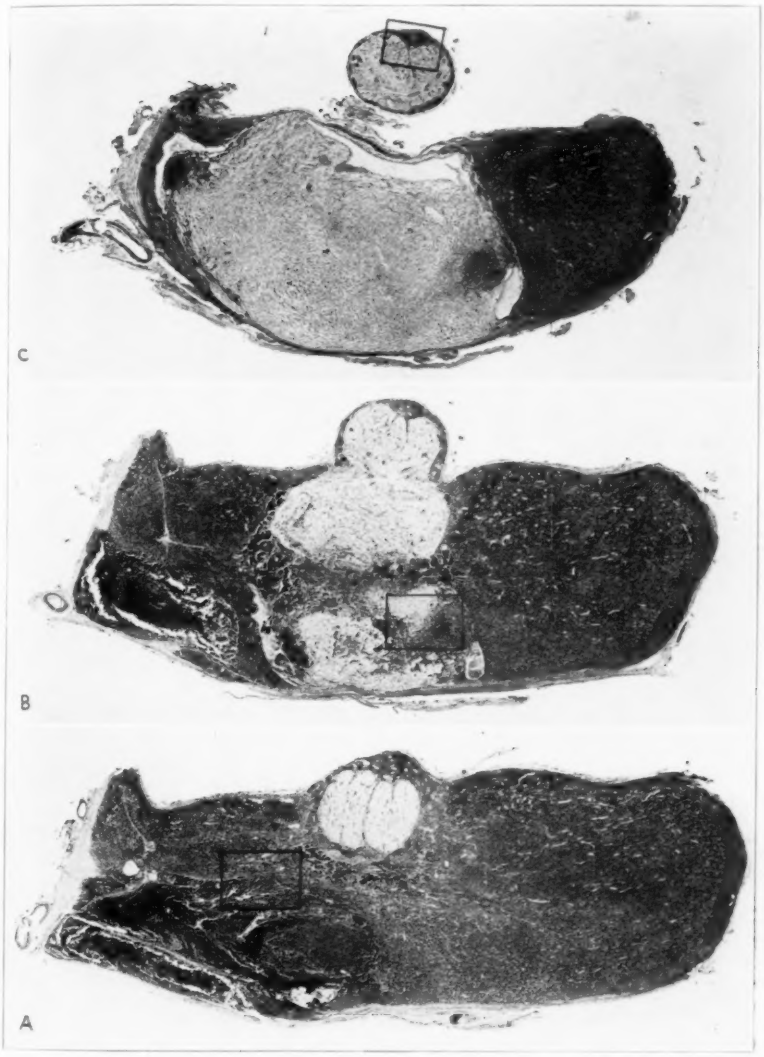


Fig. 23.—Three of the serial coronal sections (magnification × 7) showing: at *A*, greatest measured extent of the adenoma and the anterior margin of posterior lobe surrounded by pars tuberalis; at *B*, extensive basophilic invasion of posterior lobe from pars intermedia; at *C*, transsection of stalk as well as of posterior lobe, small areas of basophilic invasion being still evident at its lateral aspects.

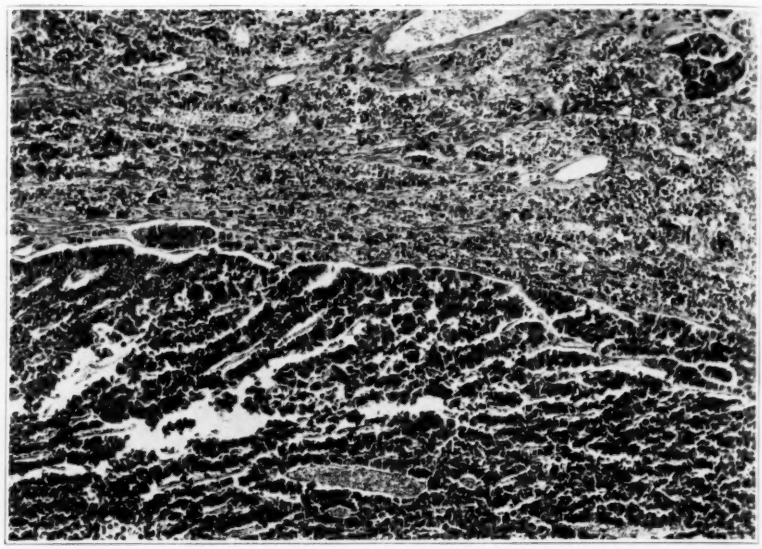


Fig. 24.—Margin of basophilic adenoma (magnification × 70) from squared area in figure 23 *A*. Note small isolated collection of basophils in upper right corner, such as occur in other parts of the lobe.

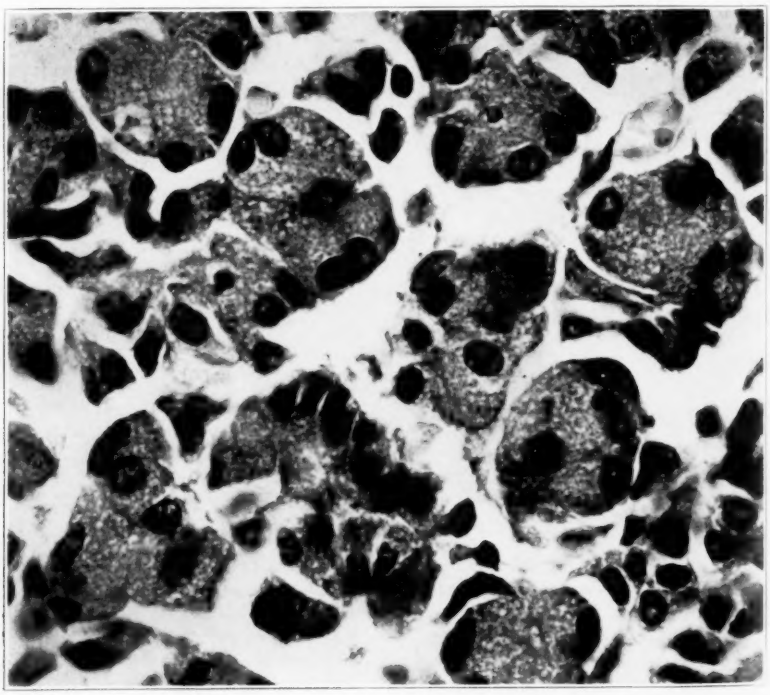


Fig. 25.—Large basophilic elements composing tumor with typical vacuolated cytoplasm (magnification × 850).

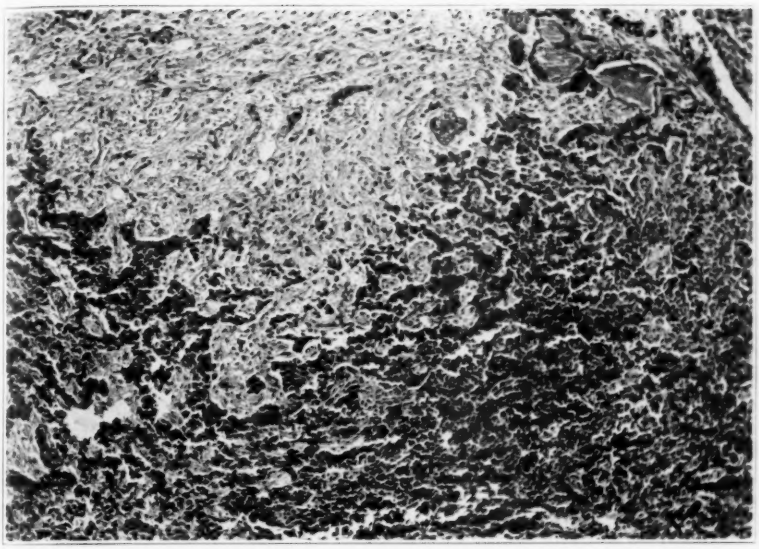


Fig. 26.—Squared area in figure 23 *B* (magnification × 70) showing invasion of the posterior lobe by cords of basophil cells from pars intermedia.

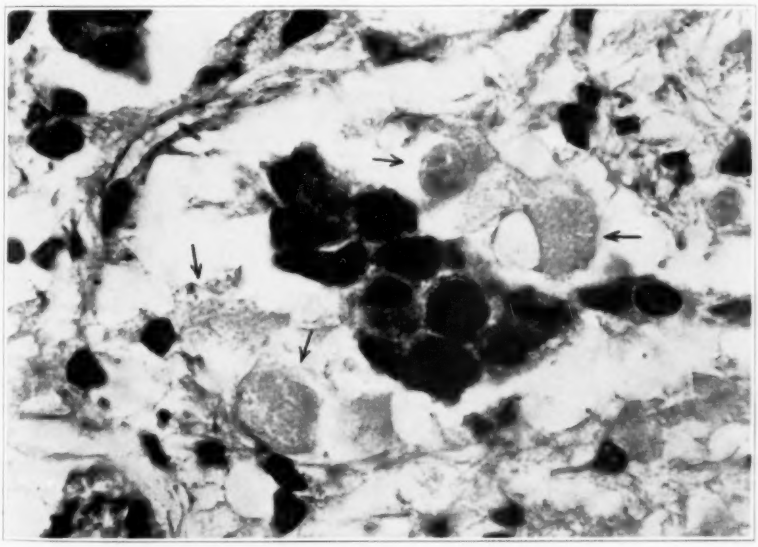


Fig. 27.—Disgorgement of ripened cytoplasm (arrows) of invading basophilic elements into loose tissue spaces of posterior lobe (apocrine secretion), the ghosts of nuclei still apparent in many of the granular masses.

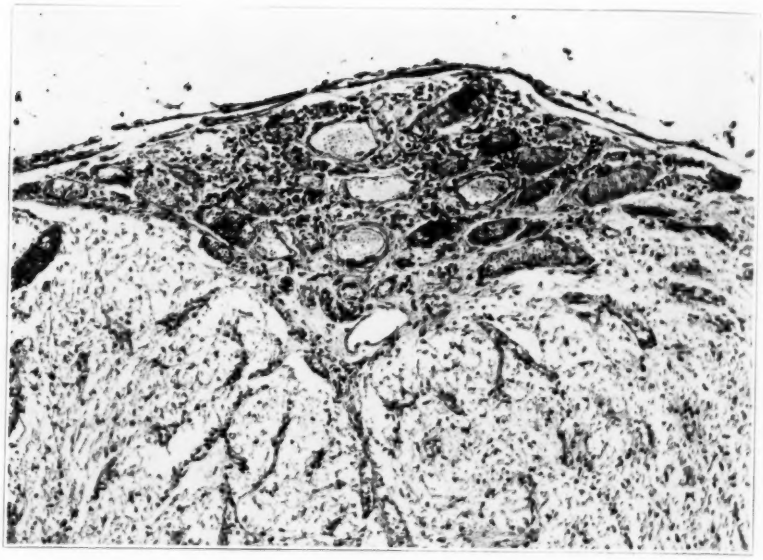


Fig. 28.—Posterior edge of pituitary stalk (cf. squared area in figure 23 C), the bundle of dilated "portal" veins passing from pars distalis through pars tuberalis to hypothalamic (chiefly tuberal) nuclei (magnification × 100).

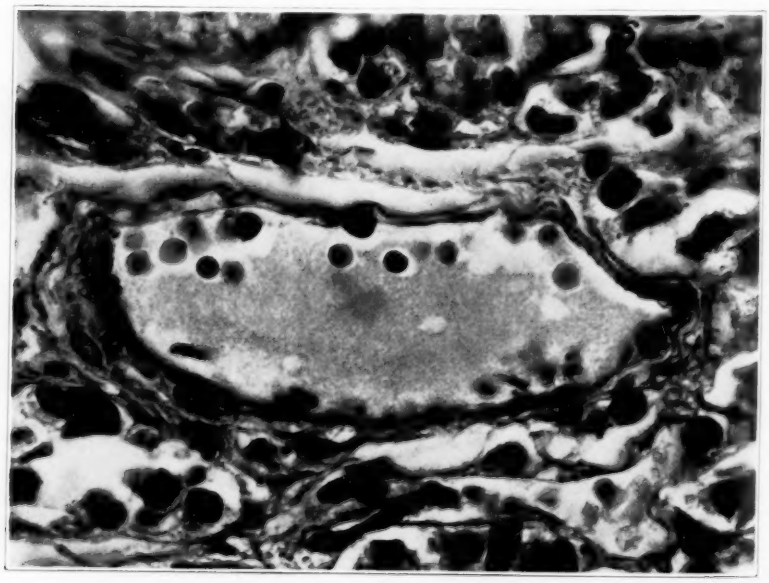


Fig. 29.—A "portal" vein in pituitary stalk so packed with the finely granular secretory product (?) as almost to exclude red blood corpuscles (magnification × 850).

How can one account for the symptomatic effect of this peculiar lesion? That it is an adenoma composed purely of basophilic elements is beyond question. But does it operate merely by pouring its specific hormone into the general circulation, or does the excess of basophilic elements that congregate around the pars intermedia and infiltrate the infundibular lobe indicate the participation of the neurohypophysis in the symptom complex? And if so, does the character of the posterior lobe secretion become modified under these circumstances or merely increased?

The attempt to answer these questions obliges us to consider: (*1*) the secondary effects of the "basophilic" hormone, whatever it may be, on the other organs of internal secretion; and (*2*) the possibility that the posterior lobe has been activated by the lesion. To this possibility we may first turn.

1. BASOPHILIC ACTIVATION OF THE NEUROHYPOPHYSIS

A more or less profuse infiltration of the posterior lobe by viable, normally staining basophilic elements from the pars intermedia has been often described, attention having been first called to it by Thom[130] (1901) who believed it to be a peculiarity of advancing age. It was noted by Erdheim[47] (1903) also as a characteristic of old persons; by Löwenstein[85] (1907) as a feature of the pituitary adenomas; by Herring[67] (1908) who found that thyroidectomy increased the cellular invasion; by Lucien[98] (1909) who distinguished the cells as basophilic elements and believed the invasion to be more pronounced in chronic maladies of the aged. It has also been discussed from various aspects by Tölken[132] (1912), by Plaut[96] (1922), and by Lewis and Lee[82] (1927), by Kraus and Traube[76] (1928), by Berblinger[19] (1927) and most recently by Zondek[137] (1933) and by Guizzetti[62] (1933).

With all this accumulative histologic evidence of the frequency of the process, little has been said of its functional significance or of its relation to an associated clinical syndrome. It was once reported as a distinguishing feature of the gland in an early case of acromegaly.[41] However, in no instance has the process been so striking as in the neurohypophysis of this patient, nor have I ever observed before the masses of hyalinoid secretion in the portal vessels of the stalk which are now known to terminate in a plexus surrounding the tuberal nuclei.*

The basophilic elements, consequently, as suggested by the conditions found in the serially sectioned gland of Miss P., may not only exercise their effects through the blood stream, but their product, possibly modified during its passage through the posterior lobe and stalk, may exercise a local effect, presumably stimulatory, on the diencephalic nuclei in whose neighborhood these veins appear to disgorge their product.

* The few sections I have of the Raab-Kraus tumor (cf. fig. *22*, case 10[76]) show also a heavy invasion of basophils apart from the tumor mass which appears to have arisen in the pars intermedia. Professor Kraus mentions this in his protocol.[76]

There is nothing revolutionary in this idea. Herring's conception[67] (1908) of an infundibular pathway for the secretion of the pars intermedia was independently advanced by Thaon[129] (1907), by Livon[84] (1908), by Cushing and Goetsch[41] (1910), and by Edinger[44] (1911) and was warmly supported by Remy Collin[37] (1928) in his monograph, "La neurocrinie hypophysaire." While these observations were for the most part based on the anatomic study of the tissues, it has recently been shown (1933) by Zondek and Krohn[138] in a series of striking experiments that the pars intermedia elaborates a pigmentary hormone, intermedin, which by a novel and delicate test can be traced through stalk, tuber, and into the fluid of the third ventricle. How many more of the several posterior lobe principles will be found to be similarly distributed remains to be seen.

To such a neurotropic effect, for want of a better explanation, may be ascribed the adiposity, the hypertension and the late vascular changes, which may now be briefly taken up one by one. While it is possible that the glycosurias that occur in these states of basophilism also belong in this same category, their separate consideration will be postponed to a later section dealing with the pancreatic islets. While much that follows is speculative, and based on the examination of this single case, it will at the same time prove, I hope, to be provocative of further study as new opportunities arise.

The Adiposity.—The rapid onset of an obesity which spares the extremities and is chiefly abdominous, while it was not pronounced in this particular patient, has nevertheless been a striking feature in all but one or two of the reported examples of pituitary basophilism (cf. table of cases). We have learned both from animal experimentation and clinical experience that a moderate degree of adiposity is a feature of pituitary insufficiency; but as Smith has so clearly shown in the rat,[115] states of extreme obesity comparable to that under consideration can be experimentally produced only by a tuberal injury.

To a presumed injury of the tuber from pressure against the dorsum sellae, Raab[100] ascribed the rapidly acquired obesity of his patient. While this might be mechanically possible with a large tumor, the explanation could scarcely apply to an unenlarged gland. The effect nevertheless may conceivably be a tuberal one, but for quite a different reason—namely, on the basis of a tuberohypophysial mechanism hyperactivated by secretory products from the pars intermedia. And the fact that many of the patients with pituitary basophilism show varying degrees of polyuria and polydipsia is not unfavorable to this interpretation.

The Hypertension.—Whatever may prove to be the cause of the acute adiposity, the attribution of the hypertension, which characterizes the clinical syndrome in all cases, to an excess of neurohypophysial secretion has much in its favor. Compatible with this view is the fact that patients with chromophobe adenomas, which serve to flatten the posterior lobe out of all recognition, invariably have a subnormal blood pressure. Heretofore, the vascular hypertension of polyglandular dis-

orders has been ascribed to an adrenal source; but the hyperplasia solely affects the cortex of these glands and the neural core of chromaffin cells which elaborate epinephrine remains, so far as can be told, histologically unaltered.

The long recognized pharmacodynamic properties of posterior lobe extracts and their relation to the utilization and elimination of water, fat and carbohydrates have only in recent years begun to be interpreted in terms of clinical experience. Hofbauer,[69] in 1918, in view of the pressor and antidiuretic effects of the extract together with the known enlargement of the hypophysis during gestation, suggested that the pregnancy toxemias, especially eclampsia, might be due to overaction of the posterior lobe. This view has received experimental support by numerous workers, culminating in the demonstration by Anselmino and his collaborators (references 4, 5 and 70) not only of an antidiuretic substance in the blood of all cases of nephropathy and eclampsia, but of a pressor substance as well when the disorders are accompanied by high blood pressure.* Naturally, the substance was looked on as a product of the posterior lobe, which we may take to mean primarily of the pars intermedia.

For many years certain Continental pathologists have given painstaking attention to the cytologic changes in the adenohypophysis in various diseases. Berblinger [18] was the first to call attention to the increase of the basophilic elements of the gland in advanced renal disease, more particularly noticeable in uremia [20]; and Kraus and Traube [50] have amplified this to include hypertension and a confusing variety of other disorders. So far as I can determine, however, neither they nor others [68] who have confirmed their observations have emphasized the significance of the basophilic invasion and resultant activation of the neurohypophysis.

Cholesteremia and Atherosclerosis.—Coincident with the acute adiposity, most of the patients with basophilic adenomas, in whom the determination has been made, have shown a moderate cholesteremia. This Kraus [78] looks on as the primary factor, the increase of lipoids in the adrenal cortex being secondary, causing in turn the multiplication of the basophilic cells in the pituitary body. However this may be—and it seems an improbable sequence—there can be little doubt of the damaging effect of the cholesteremia on the blood vessels. A deposition of cholesterol esters in the intima Ashoff looks on [9] as the starting point of atherosclerosis, while the appearance of calcium in the media is a secondary process which appears to be accelerated by active ergosterol produced by irradiation of body lipoids.

The combination of cholesteremia, therefore, with the increase of blood calcium which accompanies the osteomalacia, would seem to be a combination most favorable to the production of the vascular disease seen in these states of pituitary basophilism, the mild degree of nephritis

* Attention should be drawn to the fact that for their tests Anselmino and Hoffmann utilized the rabbit—a notoriously unreliable experimental animal.

being a secondary effect. And it is quite probable that even should the cholesteremia, as in this particular patient, not have been apparent in the later stages of her disease, the stiffening of the vessels which had taken place would in themselves have served to perpetuate her hypertension. In one or two other examples of the disease, a notable fall of blood pressure has coincided with a temporary subsidence of all other symptoms.

2. SECONDARY ENDOCRINE EFFECTS

Should the basophilic cells prove to be responsible for the gonadotropic hormone, the syndrome produced by an adenoma of these elements is scarcely what one would expect. So far as I am aware, however, the gonadotropic hormone from the pituitary body, like that from other sources, has been employed only for short time sex-maturing observations (cf. the early adolescence of Alice D., p. 516, and of Teel's case [126]), and no one has set out to learn what might be the systemic effects of its continued administration over long periods. While this will undoubtedly come to be done, let us see what interpretation in terms of the experimental laboratory can be offered in the present state of our knowledge for such effects of the three pituitary adenomas as may conceivably be ascribed to functional disturbances of subsidiary glands.

A primary adenoma of any ductless gland doubtless affects by its excessive secretion the secretory activity of all others, just as does the extirpation or pathologic destruction of any one member of the series. But a hypersecretory adenoma or a destructive process in no other gland produces such grossly evident secondary changes in the series as occur when the disorder primarily affects the pituitary body. On this fact the pathologic and experimental evidence of its dominance chiefly rests. What effect primary lesions of the subsidiary endocrine organs actually have on other members of the series is usually shown most strikingly as a reciprocal response on the part of the adenohypophysis itself, e. g., the increase of elements of certain types after thyroidectomy, adrenalectomy and castration.

Unfortunately, we have only fragmentary data regarding the gross and microscopic changes of each subsidiary organ consequent on the experimental withdrawal or increase of the two principal hypophysial hormones separately, chief attention having been paid to the gonads, the thyroid and the adrenal. The sensitivity of the gonads is well known, but the adrenal cortex and thyroid are scarcely less sensitive, as has been amply shown both in the dog and rat. A prompt shrinkage of these structures follows hypophysial extirpation, and a no less prompt hyperplasia follows the injection of prepared extracts of the growth hormone.

Clinicopathologic experience, so far as it goes, coincides with these observations. A chromophobe adenoma whose effects, as we have seen,

are comparable to a more or less complete hypophysectomy, is followed by atrophy of adrenal cortex, of thyroid and of reproductive apparatus. On the other hand, acromegaly, the clinical expression of experimental overgrowth, is associated with a notable hyperplasia of these organs, as has elsewhere been emphasized.[40]

Before entering on a more detailed discussion of these matters, it may be convenient to have before us a diagram (fig. 30), which indicates (roughly, to be sure, for want of a sufficient number of detailed weights and measurements) what gross changes the acidophilic adenomas of acromegaly, what the basophilic adenomas of the disorder

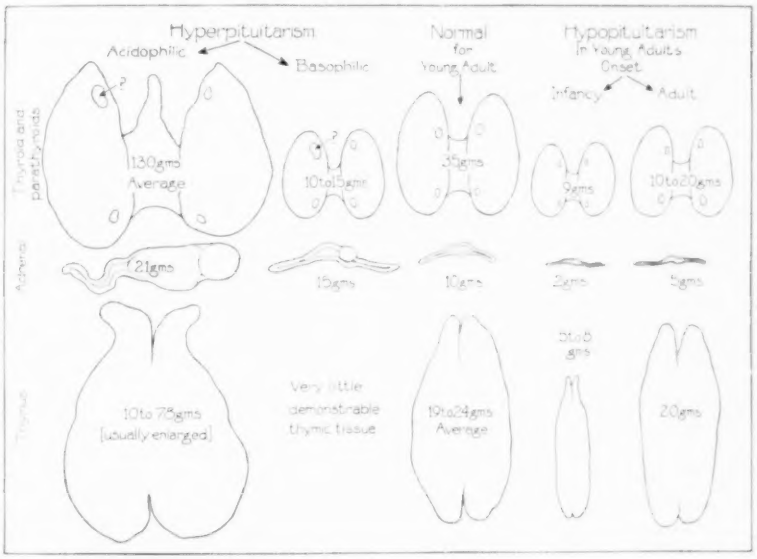


Fig. 30.—A rough diagram (capable of improvement with further data) to indicate, for comparison with the normal organs of the young adult, the secondary changes in the ductless gland series consequent on hyperpituitarism, both acidophilic and basophilic; and on hypopituitarism of young adults which has started (1) in infancy and (2) in adult life. (Reduced two-thirds from natural size.)

under consideration, and what the dual hypopituitarism of chromophobe adenomas tend to bring about. Not enough is known of the interstitial cells of the gonads to represent them in the schema, nor are sufficiently definite changes observable in the pancreatic islets to justify their inclusion.

Symptoms Referable to the Thyroid.—In these states of pituitary basophilism, the thyroid appears to be surprisingly inactive. In the case

under discussion, the gland was small and the basal metabolic rate low on the several occasions when it was tested.* This corresponds to the condition of the gland in hypopituitary states, whether clinical or experimental.

In clinical acromegaly, on the other hand, the gland becomes progressively, sometimes enormously enlarged, and many acromegalics show an elevated metabolism. This may at times be so high that the enlarged thyroid has often been operated on for assumed primary hyperthyroidism. And while this activation of the thyroid with accompanying increase of metabolic rate is usually interpreted in terms of the adenohypophysis, it must not be overlooked that posterior lobe extract and its derivatives, pitressin and pitocin, have been shown by Geiling and his co-workers [58, 61] to have, both in man and dogs, a marked effect on gaseous metabolism.

To experimental alterations of pituitary function, the thyroid, as is well known, responds promptly. Its rapid disorganization and subsequent atrophy, though wrongly interpreted, was observed in our early canine experiments. On the other hand, in experimental gigantism in the rat and dog, the gland becomes quickly hypertrophic. It is now claimed, indeed, by Junkmann and Schoeller [73, 74] that the gland elaborates a separable thyrotropic hormone, and Evans believes that convincing proof of this lies in the fact that a thyroid-stimulating property remains in the extractives after removal by precipitation of both the growth-promoting and the sex-maturing fractions.

Parathyroid Participation.—The clinical evidences of skeletal decalcification were less marked in the case of Miss P. than in many other recorded examples of the disorder. There was a history of two or three fractures without severe trauma; the roentgenologic appearance of the bones during life betrayed the mild degree of osteomalacia that was found after death, and the multiple renal calculi were characteristic of hyperparathyroidism. On the other hand, she never became round shouldered from collapse of the vertebral bodies, and no increase of calcium elimination was demonstrable at the stage of the disease when her mineral metabolism was under investigation. The glandules were found to be grossly enlarged, but this proved to be due to an interlobular infiltration with fat.

Far more is known about the internal secretion of the parathyroids and its effects than of the cells which produce it. Parathormone, in the opinion of Collip's co-workers,[131] activates the osteoclasts with consequent loss from the skeleton of its calcium phosphate, the kidneys in time becoming affected in their efforts to unload from the blood its excess of mineral salts. In hyperparathyroidism associated with adenomas of the glandules, a wholly similar process occurs, a high blood

* The reading (cf. table of cases) was said to be high in cases 3, 4, 8 and 9, but this in no instance was shown to be associated with any demonstrable hyperplasia in the thyroid when it came to be examined post mortem.

calcium with a low blood phosphorus and increase of phosphotase having been shown by J. C. Aub and his co-workers[2, 15] to be a uniformly characteristic feature of the malady. But whether in the absence of an adenoma a physiologic activation of the glandules may cause corresponding though milder effects remains conjectural for want of precise information (such as we have for the thyroid gland) regarding the histologic changes in the glandules which are an expression of functional hyperplasia.

Since no definite inter-relationship with other glands of internal secretion has heretofore been established for the parathyroids, it is venturesome on symptomatic grounds alone to suggest that we have clinical evidence of it here. With one possible exception, no abnormalities of any kind have been observed in the parathyroid bodies of persons who have succumbed to pituitary basophilism. The exception was a case reported twenty years ago, first briefly by Schmorl,[111] and subsequently more in detail by Molineus[89] together with two other examples of advanced osteitis deformans, in both of which a parathyroid adenoma was found. Naturally enough, therefore, the osteomalacia in the third case was likewise ascribed to hyperparathyroidism on the basis of an oxyphilic hyperplasia without adenomatous formation. Clinically, this case, as reported, had all the hallmarks of the malady under discussion. The large basophilic adenoma which was found post mortem was looked on as an incidental lesion playing no part in the syndrome.

Osteomalacia, indeed, has often been so striking a feature of the post-mortem findings in pituitary basophilism that the protocol of the autopsy has been largely given over to it. Nevertheless, it is rare for the process to be so marked that it could be mistaken for von Recklinghausen's generalized osteitis fibrosa. It may be that this advanced type of decalcification may require an amount of parathormone quite beyond the capacity of a simple hyperplasia and only be delivered by a functionally active parathyroid adenoma.

Unfortunately, the parathyroid glandules have not always been looked for and examined, but when this has been done an unmistakable adenoma has never been detected. And apart from the multiple skeletal lesions in the Molineus case, the only instance of a possible "brown tumor" occurring in a patient with pituitary basophilism was the pelvic lesion roentgenologically picked up in the case of Alice D., to which brief allusion has just been made (p. 516).

The Thymus.—A thorough dissection of the mass of mediastinal fat in this patient failed to detect any isolated organ, and only shreds suggestive of thymic tissue were microscopically demonstrable. Similarly, in all other cases of basophilism that came to autopsy the gland has been reported as small whenever specific reference has been made to it. To this, however, there is one notable exception, namely, the case

with many of the clinical features of pituitary basophilism reported by Leyton, Turnbull and Bratton [83] in which a cancer of the thymus was found in the absence of any pituitary abnormality.

On the other hand, the thymus may be greatly enlarged in association, curiously enough, both with chromophobe and with acidophilic adenomas. In what was probably the first case of acromegaly ever thoroughly examined post mortem, Fritsche and Klebs [55] found the thymus to be so markedly hypertrophic they were inclined to ascribe the disease to this source rather than to the less strikingly large pituitary body. Just what these hyperplastic revivals of the dormant structure signify, the Sphinx among the glands of internal secretions (if it actually is one of them) has not yet revealed.*

Pancreatic Islets VERSUS *Hypophysis in Sugar Metabolism.*—The patient, as will be recalled, came under Dr. Joslin's care because of her glycosuria, a symptom which has been even more marked in other examples of the disorder. In one instance (case 11 of an earlier report [25]) during an acute exacerbation of the malady the hyperglycemia was found to be uncontrollable by insulin. Since then, however, the glycosuria of that patient has spontaneously subsided; and as the adiposity and hypertension have also grown less, he, at the present time, in spite of the residual stigmas of the disease, enjoys reasonably good health.

Similar waves of hyperglycemia, as is well known, characterize acromegaly. In this disorder also, not only is the glycosuria difficult to control by insulin, but it may sometimes spontaneously disappear when hypopituitary symptoms ultimately come to be superimposed on the original clinical picture. In view of all this, doubts naturally arise regarding the rôle of the pancreatic islets in pituitary (acidophilic or basophilic) diabetes, for what is known as primary pancreatic diabetes shows no remissions of this sort.

Allusion has already been made (p. 489) to the peculiar state called cachexia hypophyseopriva which we observed as a sequel of our early canine hypophysectomies and which usually proved fatal. While we did not then know enough about carbohydrate metabolism to realize that this might represent a state of acute sugar deprivation (now known as hypoglycemic shock), we did soon learn that a greatly increased tolerance for carbohydrates would be shown by the animals that recovered from the operation. And we soon learned, too, that a corresponding high tolerance for sugars was characteristic of clinical hypopituitarism. It was already known that posterior lobe extracts caused glycosuria in certain animals, and we were therefore misled into ascribing the disturbances of sugar metabolism solely

* What may be the relation, if any, of the fat organ of batrachians and of hibernating mammals to the thymus I am not enough of a comparative zoologist to know. It will be recalled that in the Smiths' early report [119] on the responses of the tadpole to hypophysectomy, the thyroid, parathyroid and adrenals failed to develop, but the fat organ remained hypertrophic; injections of posterior lobe extract caused it to disappear (cf. Rasmussen [102]).

to this part of the gland.* Hence, after working over the problem at length, it was stated [69] that: "If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the hypophysial posterior lobe greatly enhances their power in this respect." So marked was the degree of tolerance for sugar, we had come to believe that a preliminary hypophysectomy might actually counteract the fatal effects of removing the pancreas, but we never got so far as to put this to the supreme test of a total pancreatectomy.

It meanwhile had been observed by Aschner [5] that after a transphenoidal hypophysectomy glycosuria could be easily produced by a piqûre of the tuber. And this was also found to be true in the course of our later efforts [134] to work out the autonomic control of the gland by tracing the pathway of neuroglycosuric discharges. That the tuberal nuclei directly controlled the neurohypophysis was then not even surmised.

New light was thrown on the question favorable to posterior lobe participation in carbohydrate metabolism, when Burn [20] (1923) discovered the antagonistic effect of insulin and neurohypophysial extracts, the latter serving to counteract the symptoms of hypoglycemia. Others promptly corroborated this observation, and it was soon found by Houssay and Magenta [72] (1924) that hypophysectomized dogs are hypersensitive to injections of insulin; and the same now proves to be true of hypophysectomized monkeys [94] and also of patients with a marked hypopituitary syndrome.

This was further amplified in an important paper (1927) by Geiling and others,[57] who showed not only that removal of the canine anterior lobe alone, leaving the posterior lobe intact, failed to cause insulin hypersensitization, but also that the hypoglycemic "shock" so easily produced by giving insulin to totally hypophysectomized dogs can be prevented by the coincidental injection of posterior lobe extract. Finally, Cowley [30] has recently (1931) demonstrated the presence in the blood of hypophysectomized dogs of a substance having a marked hypoglycemic action. All things considered, therefore, evidence abounds that the high tolerance for carbohydrates in hypopituitary states is due to an increase of the insulin content of the blood due to the withdrawal of the counteractive posterior lobe principle.

So much, then, in behalf of the neurohypophysis. What now can be said of the adenohypophysis in relation to sugar metabolism?

While it was observed that some of our laboratory dogs, in process of becoming acromegalized by injection of Evans' growth hormone, showed hyperglycemia, the problems this suggested were not pursued. They, however, have been seriously attacked in a telling series of experiments conducted during the past three years by

* In recent years it has been shown by Geiling and Eddy [59] that posterior lobe extract and its derived products, pitressin and pitocin, produce hyperglycemia; also by Nitzescu and Benetato [91] that there is a coincidental increase of inorganic phosphate in the blood.

Houssay and Biasotti [71] who have shown that diabetes fails to develop in hypophysectomized toads on subsequent removal of the pancreas. When, however, toads in this precarious state of experimental carbohydrate balance are given subcutaneous implantations of the anterior lobe of fishes, birds or mammals, they immediately become diabetic. Though this effect is less striking in hypophysectomized dogs subsequently deprived of the pancreas, they acquire a diabetes of slow evolution with long periods of remission in which hypoglycemic crises may occur. It has also been shown by the Argentine physiologists that administration of the growth hormone to normal rats and dogs will provoke glycosuria with polyuria and hyperglycemia, and they go so far as to predict the discovery of a pituitary diabetogenic hormone which plays the predominant if not exclusive rôle in carbohydrate metabolism.

There is only one way of reconciling these contradictory views regarding posterior vs. anterior lobe control over the utilization of sugar —and that is to accept them both as correct with another interpretation. This interpretation is that which has already been advanced as an explanation of the hypertension: namely, that the pars intermedia cells pass into and activate the neurohypophysis.*

But whatever may prove in the end to be the correct explanation, there is evidence at hand that extracts of both anterior and posterior lobe exercise an antagonistic effect on insulin. Whether this effect is produced by inhibition of the islets or by extrapancreatic neutralization of liberated insulin remains undetermined. From an histopathologic standpoint, while primary pancreatic diabetes is said to be accompanied in something over half of the cases by demonstrable lesions of the islet tissue, no corresponding changes have ever been convincingly described either in acromegaly with hyperglycemia or in the few instances of pituitary basophilism in which autopsy was performed.

All said and done, there is possibly no more reason why we should expect to find the islets appreciably atrophic in these maladies than to find them hyperplastic in the counter-states of pituitary deficiency in which the tolerance for carbohydrates is increased. Histopathology has its limitations, and the function of cells may conceivably be altered without recognizable change of form.

The Adrenal Participation in the Syndrome.—Hypertrophy of the adrenal cortex was one of the striking features of Miss P.'s case, as it has been of most other instances of basophilism that have had a postmortem verification. It is chiefly shown in the zona fasiculata whose cells are distended by an increase in their lipoid content. Certain

* The reciprocal effects on the hypophysis of disordered function of the pancreatic islets has received scant attention from the anatomic side. Kraus [75] described a shrinkage of the gland particularly noticeable in the pars intermedia after pancreatectomy in the cat—an observation which others failed to substantiate. Eaves,[43] on the other hand, briefly reported that prolonged injection of small doses of insulin in rabbits causes enlargement of the hypophysis and changes suggesting cellular hyperplasia, both of the pars intermedia and the pars anterior.

features of the syndrome so strongly suggest a primary hyperadrenalism it is not surprising that several of the patients in the series should have been subjected to a suprarenal exploration with unilateral adrenalectomy. And the fact that a definite though small adenoma of cortical elements has been found in one or two instances has been highly misleading.*

The basophilic elements, therefore, whatever the nature of their hormone, evidently elaborate a substance which has a highly stimulating

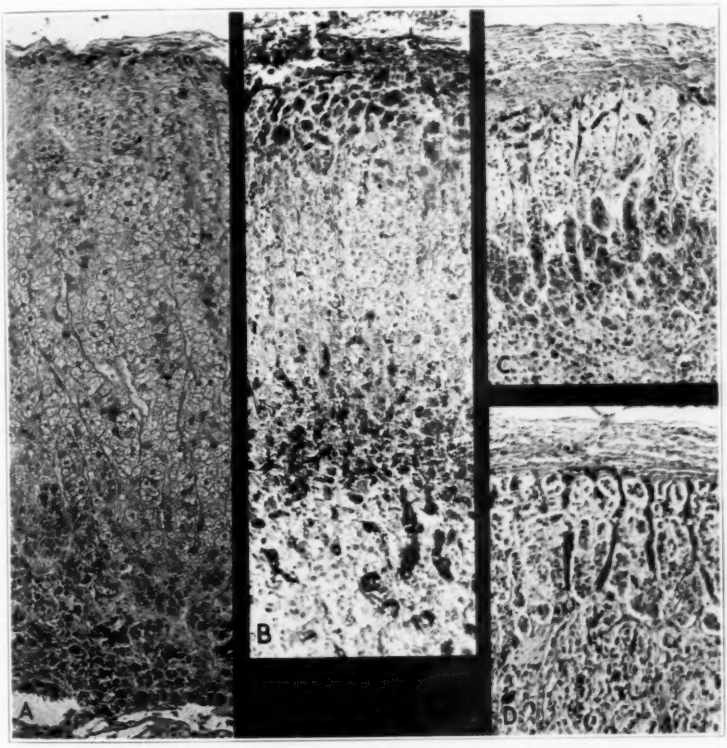


Fig. 31.—Adrenal cortex (magnification × 80) from: *A*, the case of pituitary basophilism; *B*, an acromegalic; *C*, an adult with hypopituitarism from chromophobe adenoma; *D*, an adult pituitary dwarf, aged 27.

effect on the adrenal cortex. The accompanying photograph (fig. 31) indeed suggests that the degree of hyperplasia exceeds even that produced by the acidophilic elements in acromegaly. To put to a compara-

* That an accessory para-ovarian nodule of adrenal tissue was found in this and another case of basophilism need cause no surprise in view of the embryogenic relation of both adrenal gland and reproductive apparatus to the wolffian body.

tive test the effect on the cortex of the growth principle and of a sex-maturing principle the following study (unpublished) was made a year ago at my request by Drs. Thompson and Troppoli:

For the experiment were used three groups of three immature litter-mate female rats. All nine animals were 45 days old and, with trifling variations, weighed 60 Gm. apiece. Of each group of three, one member was used as a control; a second member was given twice daily a parenteral injection of 0.5 cc. of a modified anterior lobe preparation; the third member was given twice daily 0.5 cc. of prolan-containing urine of pregnancy (the adenohypophysial gonadotropic substance would have been preferred but none was at hand).

The introitus of all three animals receiving prolan opened on the fourth day, whereas this took place in the case of the three controls and of the three animals receiving growth hormone at variable times, averaging about seventeen days.

Throughout the experiment, all animals were given an ordinary diet and were killed at the expiration of seventy-two days, during which time the three control animals had gained ca. 85 Gm., those injected with growth extract ca. 120 Gm., and those injected with prolan, an average of only 70 Gm. (one of them lost weight from a slight infection).

On the fifteenth day of the experiment, the right adrenal and ovary were removed from each of the first trio, the weights of the cleanly stripped adrenals being as follows: control, 9 mg.; growth hormone, 10 mg.; prolan, 112 mg.

On the forty-seventh day, the adrenals were removed from the second trio and gave the following weights: control, 16 mg.; growth hormone, 22 mg.; prolan, 20.5 mg.

On the fifty-second day, the adrenals removed from the third trio gave these weights: control, 20 mg.; growth hormone, 16 mg.; prolan, 27 mg.

When all nine were killed on the seventy-second day of the experiment, the animals being 117 days old, the remaining adrenal of each of the first trio weighed: control, 26 mg.; growth hormone, 24 mg.; prolan, 37 mg. The adrenals of the second trio weighed: control, 36 mg.; growth hormone, 45 mg.; prolan, 51 mg. The adrenals of the third trio weighed: control, 20 mg.; growth hormone, 14 mg. (this animal had a terminal infection); prolan, 47 mg.

While it is known that the female rat not only has heavier pituitary glands but also heavier adrenals than the male, a disproportion which increases with age, an estimate of the weight of the normal adrenal at ca. one hundred and seventeen days is given as 20 mg. (Donaldson). Needless to say, the enlargement of the organs above this weight was due solely to a cortical hyperplasia.

From this experiment, which as we shall see runs counter to the experience of others, it was deduced that among the known sexmaturing substances, prolan at least serves as an adrenocortical stimulant.

A secondary adrenal hyperplasia was shown by Evans to be one of the striking features of experimental gigantism in the rat, while an actual cortical adenomatosis was described by Putnam and his associates[39] in their first example of canine acromegaly; and though we cannot be quite sure to which of the two principal hormones this change was attributable, in view of the unpurified extract that was used in these experiments, it was probably due to that of growth.

What may be the condition of the adrenals in hereditarily dwarfed mice, in which the growth factor alone is deficient, I do not know; but

when there is dual hypopituitarism (cf. fig. 32), whether produced by a chromophobe adenoma or by an experimental hypophysectomy affecting both elements, cortical atrophy may be extreme. It was shown by Smith[115] that the weights of the adrenals of hypophysectomized rats will shrink within six days to one-half the size of the controls. What is more, the atrophic glands of these animals can be promptly restored to normal or near normal by glandular implantations, which, of course, contain both growth and sex fractions.

Evans, however, finds (personal communication) that purified growth hormone by itself will restore almost to normal the atrophic adrenals of hypophysectomized rats if treatment is instituted soon after the hypophysectomy. At the same time, he is convinced that the gonadotropic substance in pregnant-mare serum and that in the urine of pregnant women have no effect whatever on the adrenal cortex (the influence of the pituitary sex principle itself was not investigated), which controverts the Thompson-Troppoli experiments just cited.

The adrenal cortex is known to be essential to life, a bilateral adrenalectomy leading to symptoms which, even to the extreme fall in body temperature and marked loss of weight, closely resemble the acute cachexia hypophyseopriva often observed after hypophysectomy in adult dogs. Beyond this, and the fact that these symptoms may be overcome and an essentially normal condition reestablished by the injection of a cortical extract, those who have worked most extensively in the field of adrenal physiology confess[122] to scant knowledge of what the normal function of the cortical hormone may be.[123]

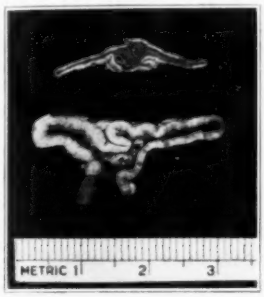


Fig. 32.—To compare (natural size) the atrophic adrenal cortex of adult hypopituitarism (above) produced by a chromophobe adenoma with the hyperplasia of pituitary basophilism (below) shown in this case; both persons approximately same age.

Of the relation of the cortex to the enclosed neuromedullary part of the gland which secretes epinephrine, we know even less than we do of the relation of the adenohypophysis to the neurohypophysis which it envelops. This admission is the more remarkable in view of the peculiar and striking syndromes which are clinically known to accompany what presumably are primary, often malignant, adenomas of the adrenal cortex and of the chromaffin tissue of the medullary substance. Characteristic features of these syndromes are hypertension, hypertrichosis, deviations of secondary sex qualities such as the masculinization of women, and even glycosuria.

While nothing is known of the reciprocal pituitary changes accompanying these clinical states of primary hyperadrenalism, an increase of basophilic elements might be anticipated if, as stated by Kraus[77] and by Berblinger,[21] these elements are notably diminished in number in cases

of Addison's disease. However this may be, when a syndrome akin to that of hyperadrenalism occurs in association with a definite basophilic adenoma, as in the case under discussion, the hypertrophic changes in the adrenal cortex, to which the symptoms are naturally ascribed, can scarcely be interpreted as other than a secondary effect.

Gonadal Effects.—We have seen that in this patient there was an early period of amenorrhea followed by a long interval of fairly normal menstruation, when again a two year period of menstrual cessation occurred and preceded death. The disorder therefore showed periods of symptomatic exacerbation and remission, just as hyperthyroidism or acromegaly may occur in successive waves of activity.

The ovaries, as recorded in the protocol, while essentially normal in appearance (fig. 33), gave evidence of follicular stimulation in the absence of luteinization resembling in this respect the ovaries of acromegaly [40] and of adult rats treated with pituitary transplants.[116] The changes in the theca interna (fig. 34), consisting of increased vascularization with an epithelioid transformation and vacuolization of the cells, are those known to occur (Corner [29]) during the period preceding maturation of the ovum.* They are looked on by many as the true interstitial cells of the ovary † and while they may possibly participate in the formation of the corpus luteum, evidence seems to favor the granulosa cells as the chief source of this body. Theca cells heavy-laden with lipoids appear in the corpus albicans only after granulosa cells have disappeared.

It is claimed [54] that the adenohypophysial gonad-influencing principle can be divided into two separable fractions, one having follicularizing and the other luteinizing properties. From the condition of the ovaries of this patient it would appear that the follicularizing stimulus is present but that the element to complete the ovulatory cycle with rupture and luteinization of the follicle is absent, thus accounting for

* Since this paragraph was written, Dr. G. W. Corner, having kindly examined the sections, states it to be his belief that the normal processes of follicular growth have been in abeyance for some time and that the ovary resembles that of a patient in the early menopausal years. While the primordial ova are in good condition, there is a striking absence of medium-sized follicles and the granular cells of all the large follicles are in the early stage of atresia, showing breakdown of the nuclei. His assumption would be, therefore, that the ovary for some reason was not receiving its normal stimulus to cyclic growth.

† The possible relation of the interstitial cells of ovary and testis to the secondary characters of sex is a complicated and disputed subject [103] which cannot here be gone into, though the bearded faces of women with pituitary basophilism suggest that something in this direction is abnormal. Collip has recently shown [28] that when the "anterior pituitary-like hormone" of the placenta is administered to hypophysectomized male rats, the usual atrophic changes in the reproductive apparatus are limited to a degeneration of the germinal epithelium, whereas the interstitial cells are increased and the accessory sex organs fail to undergo atrophy.

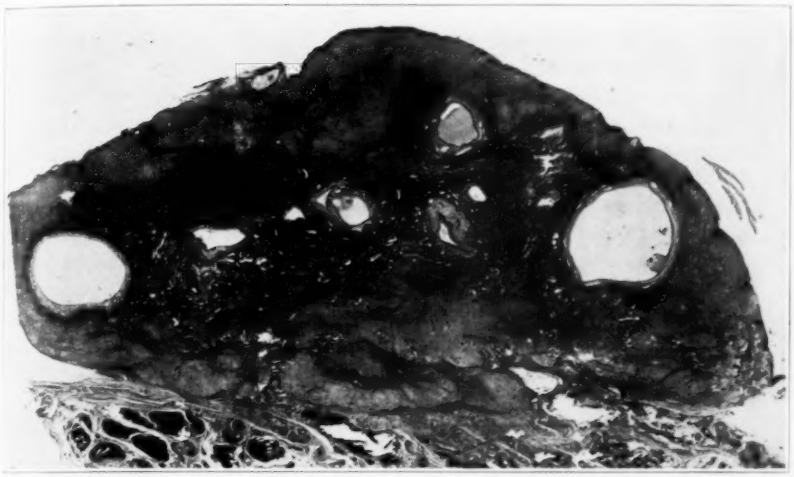


Fig. 33.—Section of patient's ovary (magnification × 5) to show surface appearance, situation and number of cysts and of corpora atretica.

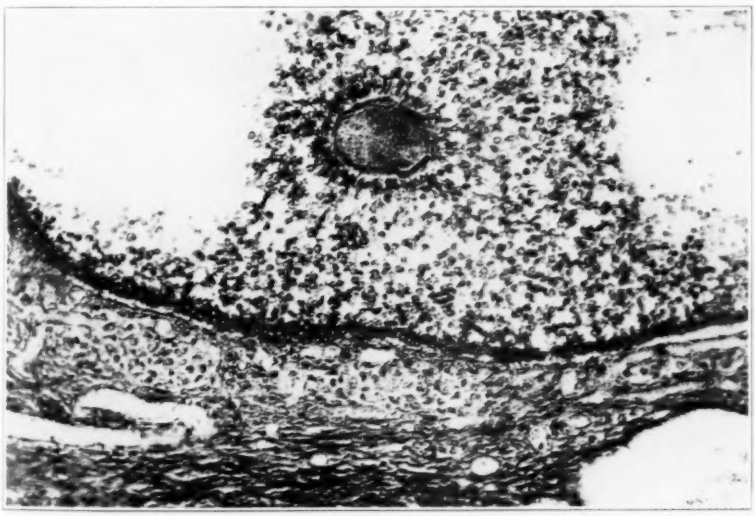


Fig. 34.—Degenerated oocyte in cumulus and active theca interna (magnification × 150).

the amenorrhea. Her urine was tested on immature female rats for gonad-stimulating properties with negative effects and the same was true of another patient (case 11 of another report [93]) in the series. On the other hand, the urine of the young girl whose photographs have been shown (cf. fig. 14) proves to have a follicularizing effect on young rabbits, so that some more sensitive recipient than the rat—the ring dove, for example [108]—may be necessary for the detection of these substances.*

The patient's small uterus with its thin atrophic endometrium was the opposite of that seen in acromegaly, both clinical [125] and experimental,[99] an enormous hyperplasia of vagina, uterus, tubes and endometrium being characteristic of these states.

As already pointed out, the evidence to show that the basophilic cells are concerned with the gonadotropic hormone is contradictory and inconclusive. Just what would be the somatic effect of prolonged administration of the adenohypophysial sex principle by itself is unknown and for the same reason it is unknown what changes would be produced in the ovary and reproductive tract by such long continued stimulus. Excessive luteinization of the ovary was shown by Evans and Long [50] (1921) to follow the prolonged administration of their original growth extract. But since the preparation then employed was not free of the gonadotropic principle, this was a complicating factor in the early experimentally produced states of gigantism both in rats and dogs and largely explains the associated gonadal effects that were observed.

Even though from the adenohypophysis of the sheep an active sex hormone may be prepared, it proves not to stimulate the ovulatory mechanism in the same way in all species, so that experimental data will scarcely be transferable to man until animals higher in the series [64] (possibly in the end, anthropoids) are employed. The whole subject has become further complicated and attention has been distracted from the pituitary hormone to the study of similar substances more easily obtained. This was brought about by Aschheim and Zondek's discovery [6] of a sex-maturing product (prolan) in the urine of pregnant women, numerous substances with similar properties having since been found in other body fluids or tissues in varying concentrations in different animals. Whether these several substances are the same as the pituitary hormone, as some take for granted, or merely serve as activators of it,[51] or represent products derived from it, or have nothing to do with it other than that their biologic effect on maturation is similar will not be known until the precise chemical formula of each comes to be worked out.

* In appraising these reactions, it should not be overlooked that those competent to pass on the question of separate follicle-stimulating and luteinizing hormones do not feel that there is adequate evidence of their separate existence.

Meanwhile, in view of their variable source of origin and variable action on different species, they have, if anything, served temporarily to confuse rather than to simplify our understanding of the direct pituitary influence on the peculiar chain of events concerned with the ripening, discharge, insemination and implantation of the ovum. It is a delicate mechanism easily disturbed. And while the condition of the ovary might be expected to give evidence of the nature of the product elaborated by a basophilic adenoma, in the present state of our knowledge its pathologic and symptomatic effects are difficult to appraise.

While fully believing that the adenohypophysis is the root of all this evil relating to disturbances of growth and sexual activity, it seems almost too much specifically to charge it with thyroid-activating, glycogenic, lactogenic, metabolizing, follicle-stimulatory, pigment-affecting, luteinizing and menstrual-initiating properties and other petty crimes of like sort for which its subordinate accomplices may well enough be responsible.

CONCLUSIONS

During the past two decades, much has been learned about pituitary dysfunction from many angles: from comparative and experimental zoology most of all; from clinical pathology a great deal; something from histologic cytology; and as yet, all too little from biochemistry to which we pin our chief hope.

Whereas the pituitary body was once looked on as a functioning whole, this idea was disrupted when Howell showed in 1898 that its blood pressure-raising effect was confined to extracts of the posterior lobe. Since then, an ever mounting number of properties suggesting separate chemical messengers have come to be ascribed to one or another subdivision of the gland—those of the posterior lobe giving acute pharmacodynamic responses, those of the anterior lobe producing their effects more slowly.

After Howell's discovery, fifteen years passed before it was found that posterior lobe extracts could control diabetes insipidus, and ten years more before the relation of this disorder to certain clusters of nerve cells in the hypothalamus was appreciated. And now after a lapse of thirty-five years, the fact that posterior lobe overactivity may be responsible for a number of hitherto obscure clinical disorders has only begun to be realized.

Attention meanwhile has been chiefly focused on the properties of anterior lobe extracts whose remarkable effects have served further to emphasize the dominance of the gland over other members of the endocrine series. Much, indeed, that has already been done in studying these subsidiary glands as isolated and independent structures needs redoing and reinterpreting. And at the same time the conception that anterior lobe, posterior lobe and interbrain work in harmony and cannot well be studied separately has been clearly demonstrated.

The pituitary adenomas have been made the subject of this lecture with the intent of drawing renewed attention to these processes as secretory "stills" which, in spite of their pathologic structure, nevertheless in all probability are elaborating an excess of the normal hormones. Not until we have learned how to incite in experimental animals an actively and continuously secreting lesion of this sort can we expect precisely to reproduce, and thereby fully to interpret the effects of Nature's prolonged experiment on man.

In order to gage what substance if any is secreted by the different adenomas, the patient's blood and urine as well as tissue from the tumor itself when available will some day have to be tested for the presence of each of the accepted as well as of the several predicated hormones of the normal gland. But only when these tests come to be more simplified than they now are will it be possible definitely to say: whether a chromophobe adenoma, like that of the dwarfed child, actually has any secretory product; whether the overgrowth in lads like those described is due to an excess of the growth principle; whether or not the blood of the acromegalic woman was flooded with a separable lactogenic hormone; and what may have been the nature of the substance elaborated by the tumor in the case of the unfortunate young woman so long victimized by pituitary basophilism.

But however much of all that I have said regarding these adenomas and their secretory effects may be fact and how much fancy, we may be sure that in the course of time the greater part of it will be modified out of all recognition. Consequently, should this second lecture on dyspituitarism prove twenty years hence to have contained a modicum of truth, so helpful to our further understanding of pituitary function in disease as was the attribution of adiposogenital dystrophy and retardation of growth to pituitary insufficiency, that would be recompense enough for me and sufficient justification, I hope, for the act of the Harvey Society.

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PERIDUODENITIS AND PERICHOLECYSTITIS

AN ANATOMIC, CLINICAL AND ROENTGEN STUDY OF ADHESIONS IN THE UPPER RIGHT QUADRANT

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DETROIT

A number of articles have appeared in recent years emphasizing the clinical significance of adhesions in the upper right quadrant. Recently the French authors, Duval, Roux and Béclère, exhaustively treated the subject of adhesions in this area in a book, "The Duodenum," in which they described anatomic, clinical and roentgen findings. They suggested operations for severance of adhesions and short-circuiting of obstructed points.

Our study arose from an attempt to apply clinically the recorded data on this subject. If the clinical and anatomic entity is as definite as has been described, it was felt that careful study of a rather large gastro-intestinal material should reveal a number of such cases.

We are concerned here with adhesions about the first and second portions of the duodenum and about the gallbladder, and their clinical significance. Lesions of the third and fourth portions of the duodenum and duodenal stasis in these portions are not dealt with.

RÉSUMÉ OF LITERATURE

Attention was first called to this subject from a clinical point of view by Dr. Robert T. Morris [1] in an address given before the Wayne County Medical Society (Detroit area) in May, 1905. He advanced the theory that these adhesions were inflammatory and of probable biliary origin. The symptoms were those of upper abdominal dyspepsia with some resemblance to those of peptic ulcer. The treatment that he advocated was separation of the adhesions and removal of the gallbladder.

Konjetzny [2] in 1913 first doubted the inflammatory origin of these adhesions, as he demonstrated them in the new-born and in infants in from 15 to 20 per cent of autopsy specimens. He stated that traction

From the Detroit College of Medicine and Surgery and the North End Clinic.
The work on simultaneous cholecystography and gastro-intestinal roentgenography was aided by the North End Clinic Research Fund.

1. Morris, R. T.: Gall Spider Cases, Am. Med. **10**:95, 1905.

2. Konjetzny, G. E.: Ueber anomale ligamentaere Verbindungen der Gallenblase und ihre klinische und pathologische Bedeutung, Med. Klin. **9**:1586, 1913.

of the colon on the gallbladder by means of the hepatocolic band would, by mechanically angulating the gallbladder neck, produce obstruction of the outflow of bile and hence colic. He also mentioned duodenopyloric stenosis due to the hepatocolic band crossing the duodenum.

Harris [3] in 1914 reported 6 cases of periduodenal bands. The symptoms in these cases resembled those of ulcer. There were also sharp attacks of pain in the upper right quadrant suggesting gallstones. He independently ascribed a congenital origin to these bands rather than the inflammatory origin proposed by Morris.

Cole [4] called attention to duodenal deformity caused by veils, and advised that in deformed cap not due to spasm, one is justified in making a diagnosis of an organic lesion which "may be due to ulcer, gall bladder adhesions of a veil, the weight of evidence being in favor of the one it most closely resembles."

Taylor [5] reported a large series of cases in which he concluded that membranes about the duodenum frequently cause partial obstruction by angulation and constriction. He stated that the best study of this region is by roentgenography, which indicates function rather than the anatomic distribution of the adhesions.

Cromarty [6] ascribed to these cases an ulcer-like picture but differing in that the pain tends to be persistent and is unrelieved by the ingestion of food. The diagnosis is made by irregular filling of the cap.

George and Leonard [7] in 1922, in a monumental work, demonstrated the relation of the diseased gallbladder as outlined by stones to the duodenum and pylorus. They emphasized the importance of the indirect signs, which up to this time were the only practical means of diagnosing cholecystitis by roentgenographic methods.

Duval, Roux and Béclère [8] in 1928 reported an exhaustive study of adhesions about the duodenum. They divide them into (1) periduodenitis of biliary origin, demonstrated by deformity of the bulb region due to cholelithiasis and cholecystitis, which may even persist after cholecystectomy, and (2) essential periduodenitis, in which no cause for the production of adhesions is found, the gallbladder, duodenum, appendix and greater omentum all being normal. In the latter group

3. Harris, M. L.: Constrictions of the Duodenum Due to Abnormal Folds of the Anterior Mesogastrium, J. A. M. A. **62**:1211 (April 18) 1914.

4. Cole, L. G.: Veils in the Right Hypochondrium and Their Differentiation from Other Organic Lesions and Spasms, Am. J. Roentgenol. **9**:137 (March) 1922.

5. Taylor, A. S.: Anomalous Abdominal Membranes: Their Influence upon the Digestive Tract, Ann. Surg. **75**:513 (May) 1922.

6. Cromarty, R. P.: Surgery of Duodenal Membranes, Canad. M. A. J. **12**: 876 (Dec.) 1922.

7. George, A. W., and Leonard, R. D.: The Pathological Gall Bladder, Roentgenologically Considered, New York, Paul B. Hoeber, Inc., 1922.

8. Duval, P.; Roux, J.-C., and Béclère, H.: The Duodenum: Medical, Radiologic and Surgical Studies, St. Louis, C. V. Mosby Company, 1928.

they placed the cases described by Morris, Harris, Cole, Cromarty, Taylor and others. Essential periduodenitis reveals itself by an aggregation of many symptoms which individually show nothing characteristic of the lesion. There are three types of symptoms: (1) those resembling the symptoms of duodenal ulcer, with pain immediately or from four to five hours after eating but unrelieved by food or alkali and associated with nausea; (2) those resembling the symptoms of biliary colic and accompanied by vomiting and perhaps even diarrhea and jaundice, and (3) nonlocalizing symptoms suggesting neurasthenia aggravated by malnutrition and progressive emaciation.

These authors have little confidence in the medical treatment of these membranes, but they stated that the mere presence of membranes about the duodenum does not warrant surgical intervention. The clinical and roentgenologic syndrome of duodenal stenosis must be present. They advise against simple section of the membranes because of their tendency to reform, and prefer instead short-circuiting operations when definite stasis is present.

Harvey[9] in 1918 made an intensive study of peritoneal folds and reviewed the literature. He gave a table showing that a cystocolic ligament was found by nine different authors in from 15 to 30 per cent of routine autopsies. He himself found the ligament in 18 per cent of cases, including only those cases in which the ligament extended up the gallbladder more than one-third its length. Ancel and Lencert[10] found the ligament well developed in 48 per cent of routine autopsies, and in some instances it completely closed the foramen of Winslow. In 1923, Nagel,[11] of the Mayo Clinic, found ligaments extending from the gallbladder to the duodenum and colon in 25.3 per cent of 150 consecutive necropsies.

Clairmont and Meyer,[12] of Zurich, divided abdominal adhesions, excluding those of florid peritonitis, into: 1. Adhesions secondary to a primary inflammation of an organ, such as ulcer of the stomach or duodenum, inflammation or stones of the gallbladder, etc. 2. Adhesions with no disease of neighboring organs, which they termed "perivisceritis." This leaves the origin of the adhesion open and avoids the impression of a spontaneous adhesion. Examples of perivisceritis are periduodenitis, pericholecystitis and perigastritis. 3. Postoperative adhesions. Congenital bands would be classified under perivisceritis

9. Harvey, S. C.: Congenital Variations in the Peritoneal Relations of the Ascending Colon, Cecum, Appendix and Terminal Ileum, Ann. Surg. **67**:641 (June) 1918.

10. Ancel and Lencert, quoted by Nagel.[11]

11. Nagel, G. W.: The Etiology and Importance of the Cystico-Duodeno-Colic Fold, Surg., Gynec. & Obst. **37**:363 (Sept.) 1923.

12. Clairmont, P., and Meyer, M.: Bauchfellverwachsungen, Arch. f. klin. Chir. **157**:474 (April) 1929.

or would need a fourth classification. These authors reported 20 personal cases of periduodenitis, in 17 of which the patients were operated on with good results and in 3 of which there was no change after the operation.

After a recital of the manifestations of abdominal adhesions by all data, Clairmont and Meyer added that a necessary part of the examination is the exploration of the psyche, 62 per cent of their patients having had a psychic defect. They concluded that even extensive adhesions after cholecystectomy do not lead to adhesion pains. Roentgenograms that indicate periduodenitis, traction, adhesions and constriction are seldom free from objections. The authors advised prudence in attaching clinical significance to the deviations found roentgenologically.

Payr, in a discussion following the presentation of Clairmont and Meyer's paper before the German Surgical Society, summarized the problem of adhesions in the following question: Are the patient's complaints caused by adhesions, are other hitherto unknown diseases present or is there perhaps a psychic condition that causes the complaints?

Renzi agreed with Clairmont that adhesions follow operations on the upper part of the abdomen most frequently, whereas cases of ileus most frequently follow operations on the lower part of the abdomen, particularly in the pelvis.

In summary, then, there is no disagreement with the fact that these adhesions occur frequently. Whether they are of congenital or of inflammatory origin has involved dispute. There is also considerable disagreement as to whether they cause symptoms. Most of the articles record cases in which symptoms have been produced and operations resorted to, but the follow-up observations in some of the cases recorded leave doubt as to the permanence of the improvement and the psychic balance of the patient.

Our plan of study included: (1) anatomic data derived from autopsy, (2) roentgen study of the right upper quadrant by simultaneously filling the gallbladder and duodenum and (3) clinical investigation.

ANATOMIC DATA

It was considered essential from the very first to distinguish between congenital membranes in the upper right quadrant, the presence of which is mentioned in a somewhat "step-motherly" fashion by the anatomists, and true inflammatory adhesions. With this in mind a series of 54 adult specimens were dissected. Eleven of these were examined at autopsy.[13] The remaining 43 were cadaver specimens,

13. Through the courtesy of Dr. Osborne A. Brines, pathologist to the Receiving Hospital.

in which the condition of the abdominal cavity was examined previous to dissection.[14] Table 1 summarizes the results of these examinations.

From these dissections we can describe the normal anatomic relation of organs and membranes in the upper right quadrant as follows (fig. 1 *A*):

The lesser or gastrohepatic omentum attaches the lesser curvature of the stomach to the liver. Its right lateral margin generally reaches to only the first or second centimeter of the duodenum, i. e., as far as the portal vessels. It then winds around the vessels and is reflected backward and to the left to form the anterior layer of the lesser

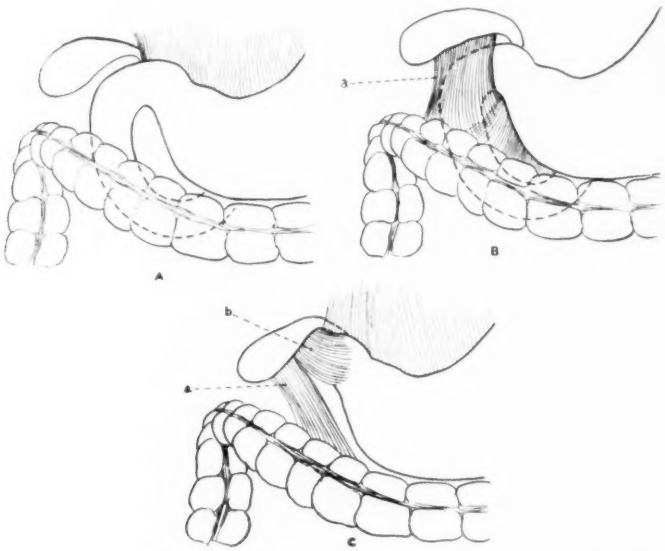

Fig. 1.—*A*, normal relations in the upper right quadrant; *B*, drawing showing (*a*) cholecystocolic fold; *C*, drawing showing (*a*) cholecystocolic fold and (*b*) cholecystoduodenal fold.

peritoneal sac. As it winds about the portal vessels it becomes the anterior boundary of the foramen of Winslow.

If the lateral margin extends further to the right it invests the gallbladder neck above and the first and second portions of the duodenum below, forming the cholecystoduodenal fold (9 cases). If it is continued still further to the right it invests the gallbladder fundus above and the transverse colon below, forming the cholecystocolic fold

14. Through the courtesy of Drs. C. F. McClintic and Watson Beach of the anatomic department of the Detroit College of Medicine and Surgery.

(14 cases). The cholecystocolic fold is a definite thin flat membrane which lies in the plane of the gallbladder, most frequently almost in a sagittal plane. Below it inserts and fuses with the anterior layer of the greater (gastrocolic) omentum; above its extension attaches the gallbladder fundus to the liver, and a further prolongation to the right is attached to the liver itself (fig. 1 *B*). In 5 cases a band was found running from the colon below, attaching above to that portion of the liver behind the gallbladder and not investing the gallbladder, a hepatocolic fold. All possible variations of these folds were seen, as will be noted from the table.

It will be noted from figure 1 *A* that the transverse colon normally crosses the descending duodenum at its midportion. The duodenum in this situation is very thin-walled and collapsible. In autopsy specimens it is usually impossible to distinguish it from the retroperitoneal tissue by rolling under one's finger or by simple inspection. If, however, one forces some air into it from the stomach, its outline will be visible.

TABLE 1.—*Membranes in the Right Upper Quadrant in Fifty-Four Cadaver and Autopsy Specimens*

	Number of Cases	Per Cent
No pericholecystic membranes	22	41
Congenital membranes	29	54
Cholecystocolic plus cholecystic duodenal	8	
Cholecystoduodenal	1	
Cholecystocolic	14	
Hepatocolic	5	
Hepatocolic plus cholecystocolic	1	
Inflammatory adhesions	3	5
Of biliary tract origin	2	
Of pelvic inflammatory origin	1	

In this situation, therefore, it is easy for pressure of the transverse colon, especially if distended, to occlude the duodenum. Duval, Roux and Béclère laid great stress on this anatomic arrangement, stating that this is a frequent cause of duodenal stasis.

In view of the frequency with which the cobwebs were found unrelated to other pathologic changes in the upper right quadrant, their presence in the new-born and in infants and their almost constant anatomic arrangement, it is difficult for us to ascribe clinical significance to them. The anatomic relation of the colon to the gallbladder by traction of adhesions and to the duodenum by pressure on its second portion may explain why patients with malfunction of the gallbladder and duodenal disease obtain relief from emptying of the colon by cathartics, enemas and the horizontal position.

It is important, however, that these cobwebs be borne in mind and recognized: (1) to realize their frequency and therefore, in an exploration of this region, not to be misled into believing that they are inflammatory, a cause of symptoms and an indication for removal of the gallbladder; (2) to distinguish them from the inflammatory adhesions,

There were 3 such cases in this series, 2 of cholecystic origin and 1 of pelvic inflammatory origin. This last case, in a colored woman, was interesting. The entire pelvis was frozen into a mass of adhesions, the uterus being retroverted and fixed. There were numerous filmy adhesions, not in definite bands, uniting the colon to the under surface of the liver and the anterior wall of the abdomen, the colon to the gallbladder, the gallbladder to the duodenum and the stomach to the under surface of the liver. After separating these adhesions a normal anatomic relation of the lesser omentum was found, with a well marked foramen of Winslow and a normal gallbladder, indicating the absence of congenital membranes.

ROENTGEN STUDY

In an attempt to demonstrate the changes in the contour of the cap and other viscera as a result of pericholecystic and cholecystic diseases, we examined roentgenologically a number of patients by simultaneously filling the gastro-intestinal tract with barium while the gallbladder was

TABLE 2.—*Data on Simultaneous Visualization of the Gallbladder and Gastro-Intestinal Tract*

	Number of Cases
Gallbladder seen with stomach and duodenum	38
Gallbladder seen with colon	31
Gallbladder seen with stomach or colon	55
Stone shadows seen with stomach and duodenum	6
Deformed gallbladder seen with stomach and duodenum	2

filled with opaque dye. The anatomic relationship between the stomach, duodenum, bowel and gallbladder was made out satisfactorily in 55 cases (table 2).

Of these there were 6 cases in which positive or negative gallstone shadows were seen and 2 in which the gallbladder was deformed. The remaining 47 were normal.

It is obvious that adhesions cannot be studied in the majority of cases of cholecystitis by this technic, as the gallbladder cannot be visualized. The exceptions to this are the cases in which positive or negative stone shadows are found.

In the first group of cases the position of the stomach and duodenum as related to the gallbladder was studied. The gallbladder was usually found lying to the right and close to the duodenal cap and pylorus. In a very small percentage of cases the gallbladder was distant from the cap. In one instance this separation was 5 cm. On the whole, the relationship was quite constant, more so than the relationship to the vertebrae given in anatomic textbooks.

An attempt was made to apply Whittaker's technic of fluoroscopic examination of the stomach, duodenum and filled gallbladder. The

latter could not be visualized by fluoroscopy in enough cases to make this a practical procedure. However, it was possible to make use of one sign, namely, localized tenderness over the gallbladder, when the latter could be seen.

In a few cases a normal gallbladder, as demonstrated by a normal cholecystogram, produced a "seat" or impression on the duodenum. Conversely, the diseased gallbladder often failed to produce a seat. However, a seat was seen in many cases of cholecystitis, so that the presence of a seat, although not pathognomonic of cholecystitis, still may be suggestive of disease of the gallbladder.

We then studied the relationship of the gallbladder to the colon and intestines. This was done by examining the patient five hours after the barium meal, twenty-four hours afterward and after the opaque enema. The gallbladder dye was usually given at night before the patient appeared for this test. Examinations were made in the prone and upright position. The relationship of the gallbladder to the colon was fairly constant. It rested on the transverse colon about 2 or 3 cm. to the left of the hepatic flexure. It usually accompanied the colon upward in the prone position and downward in the upright position, although in 1 case the gallbladder extended below, and in another it was 3 cm. above, the colon. In some cases the gallbladder as well as the colon was found in the pelvis when the patient was upright. In most instances there was an excursion of 4 or 5 cm. between the upright and prone position.

Formerly a high hepatic flexure was considered to be one of the indirect signs of disease of the gallbladder. This study clearly demonstrated that there is no basis for such a belief, for the liver, gallbladder and colon are closely related and our anatomic study shows that normally some adhesions may be present. Also there frequently exist cholecystocolic and hepatocolic bands. A high hepatic flexure may indicate that the liver does not drop freely when the patient is in the upright position, but this has no bearing on cholecystic disease.

Some data were accumulated to see if, by making the Graham-Cole test on the day the colon or stomach was studied, a day could be saved in the duration of the examination. It was found that this was impractical, as the gallbladder was partially covered by the colon, stomach or duodenum. However, some interesting roentgenograms were obtained, which showed the entire *"Wetterwinkel"* (weather-corner of the abdomen or upper right quadrant), including the stomach, duodenal bulb, hepatic flexure of the colon and gallbladder.

In the 2 cases showing a deformed gallbladder no abnormal adhesions to the surrounding viscera could be made out.

Briefly, then, the simultaneous method is valuable in demonstrating the anatomy of the upper right quadrant. Theoretically it should be

ideally suited to showing adhesions in this region. Practically, however, the latter use can be made only in the relatively few cases in which the diseased gallbladder can be visualized (by the presence of positive or negative shadows).

CLINICAL INVESTIGATION

All gastro-intestinal cases in which a roentgenologic study was made at the North End Clinic in 1930 and 1931 were observed carefully for

Fig. 2.—Roentgenogram showing "Wetterwinkel" (weather corner) with stomach, duodenum, gallbladder and colon.

evidence of adhesions in the upper right quadrant in the routine examination. In this period a gastro-intestinal study and a Graham-Cole test were made in 323 cases, a gastro-intestinal study but no Graham-Cole test in 21 and a Graham-Cole test but no gastro-intestinal study in 68.

It was thought that with adequate clinical data, combined with the roentgenologic observations, a study of this material should reveal a number of cases of pericholecystitis and periduodenitis. These cases

were carefully reviewed, with the following points in mind: (*a*) to determine whether a deformed gallbladder indicates adhesions in the upper right quadrant; (*b*) to study duodenal deformity with special attention to the causes, and (*c*) to determine the frequency and type of duodenal deformity in all cases of disease of the gallbladder seen in the last four years at our clinic.

(*a*) *Deformed Gallbladder.*—Of the 391 gallbladders studied roentgenologically, 15 were deformed, an incidence of 4 per cent. A review of these cases showed that they were associated with the following clinical conditions: chronic cholecystitis, 4 cases; postoperative adhesions after cholecystostomy, 1 case; duodenal ulcer, 2 cases; colonic or appendical disease, 7 cases, and psychoneurosis (normal gastro-intestinal tract), 1 case. A kinking deformity of the gallbladder seen in one roentgenogram may be found to have disappeared in a subsequent roentgenogram.

TABLE 3.—*Causes of Duodenal Deformity*

	Number of Cases	Per Cent
Duodenal ulcer	22	42
Duval type of deformity with cholecystitis	9	17
Duval type of deformity with syphilis, (syphilis of the liver)	2	4
Duval type of deformity with nondescript symptoms	10	19
Irritable cap with cholecystitis	3	6
Irritable cap with nondescript symptoms	6	12
Total	52	100

From these figures it will be seen that in only one third of the cases of deformed gallbladder was cholecystitis of clinical degree present; in approximately one half of the cases no pathologic changes were present in the upper right quadrant.

The diagnosis of pericholecystic adhesions derived from a deformed gallbladder should arouse the thought not only of inflammatory adhesions due to cholecystitis, but also of congenital membranes, artefacts and adhesions due primarily to duodenal disease. Deformity of the gallbladder per se is not of diagnostic but only of suggestive importance, and in the absence of confirmatory data should have little significance.

(*b*) *Deformed Duodenum.*—Table 3 shows an analyses of all cases of deformed duodenum found in the two year period. There were 52 cases shown in the 344 gastro-intestinal roentgenograms, an incidence of 15 per cent.

There are four types of duodenal deformity: (1) niche, pathognomonic of ulcer (Haudek-Akerlund); (2) constant deformity—the filling defect of L. G. Cole, probable ulcer; (3) shifting deformity of Duval—periduodenal adhesions; (4) irritable cap—spasm of local or distant origin.

Duval's deformity is differentiated from ulcer deformity in that the latter is constant in any one segment of the cap, whereas the former is shifting. Duval's deformity is differentiated from irritable cap in that in the former the cap is filled, but the deformity occupies a varying segment of the cap and is still irregular after atropine. Irritable cap, on the other hand, may fill poorly at times and be well filled at others; when filled, the contour is normal. Atropine will help to complete filling.

There were many more cases of irritable cap than are listed here; the ones included were thought at one time to be due to organic disease in the region of the cap, but further clinical and roentgen observation enables us to place them definitely in the functional group.

Of the 52 duodenal deformities, ulcer accounts for about 40 per cent; cholecystic disease, for about 25 per cent. This group represents periduodenal bands or irritable caps. The primary pathologic change here is in the gallbladder, and the periduodenal lesion is incidental.

The remainder, approximately 30 per cent, represents a group in which no ulcer or pathologic change in the gallbladder could be demonstrated. The duodenal deformity is shifting and inconstant. There is no duodenal stenosis or retention. The symptoms do not fit the roentgen observations, the final diagnosis in these cases being constipation, psychoneurosis, etc. No clinical entity could be built up from the symptoms in these cases. Our impression is that the periduodenal lesion is not significant clinically.

In general, the periduodenal adhesions have the same relation to duodenal disease as have pericholecystic adhesions to disease of the gallbladder; in the presence of normal duodenal function we can disregard the periduodenal deformity. It is necessary to bear in mind, when discussing periduodenal adhesions, that they may have their genesis in other organs than the duodenum, i. e., the gallbladder, the colon, congenital bands, abdominal lymph glands, inflammations, etc.

(*c*) *Disease of the Gallbladder.*—A study was made of all the cases of definite biliary disease seen in the clinic during the four year period from 1928 to 1931 inclusive. Some of the cases of cholelithiasis had to be omitted from this study because there were no accompanying gastro-intestinal roentgenograms. The high ratio of cholelithiasis to cholecystitis (24:42) is accounted for because only cholecystitis with definite clinical and roentgen findings was included. The cases of cholecystitis were diagnosed at operation or showed a definite clinical history, two oral Graham-Cole tests with a nonfilling gallbladder and a negative gastro-intestinal roentgenogram.

Table 4 represents a summary of the duodenal findings in disease of the gallbladder.

It will be seen from table 4 that in 13 cases, or approximately 20 per cent, there was definite duodenal deformity, presumptively from periduodenal adhesions of biliary origin. In 7 of these cases (4 of the cases of cholecystitis and 3 of those of cholelithiasis) the duodenal deformity was of such an extent that from the roentgen indications in the duodenum alone a diagnosis of duodenal ulcer would surely have been made, and in several cases this diagnosis was made until the biliary lesion was uncovered. One patient had a 20 per cent gastric residue at five hours; another showed a widened pyloric ring. It is difficult to distinguish these cases from those of ulcer by gastro-intestinal roentgenograms, but if we know that biliary disease is present (demonstrated by positive or negative shadows, or a nonfilling Graham-Cole test) we can discount the duodenal findings. The possibility of a multiple lesion is present, but the condition warrants removal of the gallbladder in any event.

TABLE 4.—*Summary of Duodenal Findings in Disease of the Gallbladder*

	Cases of Cholelithiasis	Cases of Cholecystitis	Total	Percentage
Normal duodenum	18	28	46	69.7
Irritable cap	0	4	4	6
Gallbladder seat	1	1	2	3
Filled ampulla of Vater	0	1	1	1.5
Deformed duodenum (periduodenitis)	5	8	13	19.8
Total	24	42	66	100

CONCLUSIONS

An attempt was made to apply clinically information on adhesions in the upper right quadrant in cases observed in the last two years.

The upper right quadrant abounds in membranes, as demonstrated in routine examination of cadavers. A knowledge of the presence and frequency of these adhesions is necessary to prevent too much importance being ascribed to them.

Simultaneous visualization of the gallbladder, stomach and duodenum is a method that adds little to the study of these adhesions. Where the adhesions are of biliary origin the lack of filling of the gallbladder makes simultaneous visualization infrequent.

Pericholecystic adhesions, as revealed by a deformed gallbladder, seem to be of little pathologic significance unless there is accompanying definite evidence of biliary disease.

About 20 per cent of the cases of definite cholecystitis and cholelithiasis show a shifting or definite deformity of the cap. In these cases the study of roentgenograms of the gallbladder is much more illuminating than study of the cap deformity.

The three common causes of cap deformity were found to be ulcer, cholecystitis and "essential periduodenitis." The last-mentioned diagnosis is made after excluding the two others.

Minor cases of periduodenitis occur frequently. In our experience they give rise to no tell-tale clinical syndrome. They can be recognized by means of roentgenograms, which show a duodenal deformity, usually of the shifting type, and are unassociated with stenosis or stasis. The condition does not call for surgical intervention. An acquaintance with the condition is desirable, however, to prevent its being mistaken for more serious disease in the upper part of the abdomen.

Major cases of essential stenosing periduodenitis (excluding those of biliary origin) occur rarely and are of clinical significance. We were unable to find any proved cases in our material in the past two years.

ACROPACHY

SECONDARY SUBPERIOSTEAL NEW BONE FORMATION

HENRY M. THOMAS, Jr., M.D.
BALTIMORE

Hypertrophic pulmonary osteo-arthropathy, as the syndrome is commonly designated in this country, has recently been observed under circumstances different from any heretofore described. A patient whose history I shall give in some detail returned to the clinic following an operation of subtotal thyroidectomy, presenting most exaggerated clubbed fingers and swelling of the lower part of the legs. Roentgenographic studies of the bones revealed a remarkable picture of subperiosteal new bone formation, involving most of the long bones of the skeleton, but showing a change in the bones of the hands which had not been seen by the clinicians or the roentgenologists at the Johns Hopkins Hospital. Since finding in an article by Holthusen[1] the print of an x-ray picture of a hand showing similar changes, I have come across quite a number of articles, particularly in the German literature, which discuss this condition at great length. The cause of the change in the bones remains obscure, but the case to be reported throws new light on the etiology, and for that reason seems to me to be of unusual interest.

REPORT OF A CASE

History.—W. C., a colored man, aged 22, was admitted to the Johns Hopkins Hospital on Nov. 30, 1926. For two years previous to his entrance to the hospital the patient had suffered from increasing nervousness. This was associated with a tremor which, after about nine months, caused him to abandon his work as a painter. At this time palpitation of the heart was annoying and often kept him awake at night. He was restless. Although he was becoming noticeably thinner, his neck increased in size, and he changed to a larger collar on three separate occasions. His eyes bulged. In September, 1926, he had an attack of tonsillitis which kept him in bed for three weeks and left him with marked shortness of breath on exertion, swelling of the ankles in the evening (although they were quite normal by morning) and a cough with yellow sputum. The cough, combined with a ringing in the ears, prevented sleep for about three weeks before admission. He thought that in the past two years he had lost alto-

Read before the American Climatological and Clinical Association, May 7, 1932.

From the Medical Department and the Thyroid Clinic of the Johns Hopkins Hospital.

1. Holthusen, H.: Ueber einige Besonderheiten der Osteoarthropathie (Periostitis hyperplastica) bei Heranwachsenden, Beitr. z. path. Anat. u. z. allg. Path. **77**:318, 1927.

gether 65 pounds (29.5 Kg.), although his appetite had been good. He had had a moderate diarrhea for the last two months. During the month of August he took 1 drop of iodine a day without apparent effect on his condition.

The past history was uninteresting, except for frequent attacks of colds and a case of gonorrhea five years previously (1921). There was no history of primary or secondary syphilis.

Examination.—Physical examination, made by medical intern J. H. H., showed that the temperature was 99.8 F.; the pulse rate was 124; the respiratory rate was 28; the blood pressure was 156 systolic and 78 diastolic; the height was 5 feet and 8 inches (172.7 cm.); the weight was 110 pounds (49.9 Kg.).

The patient was more than 40 pounds (18.1 Kg.) underweight; he appeared emaciated. He was restless and had a staring expression.

The skin was hot and moist; the nail beds were pale.

There was a fine tremor of the fingers. There was no clubbing of the fingers, evidence of weakness or tenderness over any bone or joint.

There was a deviation of the third thoracic vertebra to the right. The ankles were moderately swollen, with pitting edema which extended over the tibiae. The edema of the ankles was rather firm and pitted with difficulty in spite of marked swelling.

No lymph glands were palpable, except one in the right groin, which was 1.5 by 1 cm.

The patient had marked exophthalmos; there were jerky movements and a marked lid-lag. Convergence was normal. There was tremor of the closed eyelids, with widening of the palpebral fissure on focusing vision. The pupils reacted normally. The eyegrounds were normal.

The nasal septum was intact.

The teeth were in good condition.

The tonsils were large; there was a mucopurulent discharge on the postpharyngeal wall.

The thyroid gland was markedly enlarged, more so on the right than on the left. There was a palpable thrill over the right upper pole, and a to-and-fro murmur was heard over the gland. The supraclavicular fossa was filled by the thyroid gland.

The lungs were clear; no râles were heard.

The right border of the heart at the second interspace was 5 cm. from the midline; that at the third interspace, 6.5 cm., and that at the fourth interspace, 7 cm. The left border of the heart at the second interspace was 5 cm. from the midline; that at the third interspace, 7 cm.; that at the fourth interspace, 8.5 cm., and that at the fifth interspace, 10 cm.

The pulse was bounding, quick and regular in force and rhythm. The apex was heaving. No thrill was felt, and no murmur was heard.

The abdomen did not contain masses, and was not tender. The liver was not felt; the dulness extended 1 cm. below the costal margin. The spleen was not felt.

The genitalia were normal.

The reflexes were equal and active. There were no disturbances of sensation.

Laboratory Studies.—A blood count showed: red cells, 3,320,000; hemoglobin, 60 per cent; white cells, 7,610. A differential count showed: polymorphonuclear neutrophils, 73 per cent; polymorphonuclear eosinophils, 1 per cent; small monocytes, 11 per cent; large monocytes and transitionals, 14 per cent; unclassified cells, 1 per cent.

There was slight anisocytosis; the platelets looked normal.

Examination of the stool gave negative results.

The urine had a specific gravity of 1.018; the reaction was acid; it contained albumin (+), but no sugar. Microscopic examination showed a few white blood cells.

On December 1, a teleoroentgenogram showed that the right border of the heart was 6 cm. from the midline, and the left border, 8.5 cm.

Roentgen examination of the chest did not show evidence of a substernal thyroid. The lungs were clear except for a nontuberculous infiltration at the base of the right lung. The heart was a trifle enlarged, particularly the second curve to the left.[2]

Fig. 1.—Diffuse goiter with hyperthyroidism, before operation.

Treatment and Course.—December 2: The basal metabolic rate was + 59 (poor test). The temperature was 101.8 F. (rectal); the weight was 110 pounds (49.9 Kg.).

A gynergen (ergotamine) test caused no subjective discomfort.

An electrocardiogram showed a rate of 110 and a P-R interval of 0.16 second. The mechanism was normal.

Digitalis, 0.9 Gm., was given in one day. Then 0.2 Gm. was given once a day for fourteen days.

December 5: Compound solution of iodine, 30 minims (1.9 cc.), was given on this day and every day afterward for twelve days.

December 11: A blood count showed 4,450,000 red cells and 78 per cent hemoglobin.

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2. Parkinson, J., and Cookson, H.: The Size and Shape of the Heart in Goitre, Quart. J. Med. **24**:499 (July) 1931.

December 15: The basal metabolic rate was +41 per cent (poor test). The temperature was 99 F. (rectal); the weight was 127 pounds (57.6 Kg.).

December 17: Digitalis and compound solution of iodine were discontinued. Ergotamine, 0.5 mg., was given twice daily for two days without effect.

December 19: Compound solution of iodine, 30 minims, was given on this day and every day afterward for nine days, without a change in the pulse rate (120).

December 28: Subtotal thyroidectomy was performed. The gland was hard and slightly irregular, but was rather vascular.

The pathologic examination revealed changes characteristic of exophthalmic goiter.

The patient had a severe postoperative reaction, with a temperature of 105 F. and a pulse rate of 184 for two days, after which the temperature and pulse rate

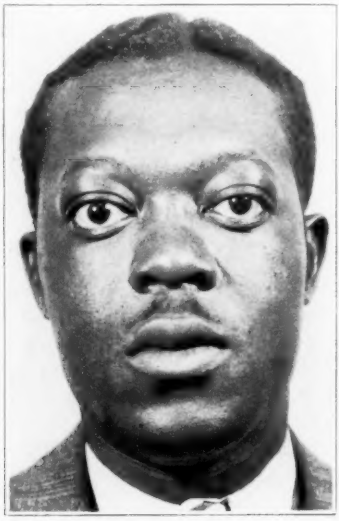

Fig. 2.—Two years after subtotal thyroidectomy.

gradually fell in five days to normal, for the first time during the patient's stay in the hospital.

Jan. 15, 1927: The basal metabolic rate was —3 per cent. The weight was 136 pounds (61.7 Kg.).

January 16: The patient was discharged from the hospital improved.

Following discharge from the hospital, the patient moved to Chicago and was not seen again until Feb. 15, 1929.

Interval History.—After leaving the hospital in 1927, the patient lived for several weeks in Baltimore and for a few months in New York City, then he went to Chicago. He had not worked. Eight months after leaving the hospital he began to notice that whereas his ankles had theretofore been a little swollen at night, they were staying swollen constantly and were enlarging. About the same time he noticed that the ends of his fingers were enlarging and becoming curved, although they were not painful. The swelling of his fingers and ankles progressed slowly until at the time of the second examination it involved the wrists and extended

from the ankles to the knees, leaving the feet unaffected. The only treatment had been rubbing with alcohol. The patient complained of no other symptoms, except that his eyes bothered him occasionally when he read. There had been no pain except on vigorous movement of the hands and legs; this pain had, however, been the cause of his not working. He had gained about 30 pounds (13.6 Kg.) in six months after leaving the hospital, but had lost weight since then.

Second Examination.—Physical examination, which was made by me, showed that the patient was well nourished.

The skin was dry. The palms were slightly moist; the axillae were quite moist. The hair was normal in texture; there was a slight thinning over the crown.

The patient had marked bilateral exophthalmos. The upper lids were slightly swollen. Convergence was poor.

Fig. 3.—Clubbed fingers, with swelling of the soft parts symmetrically distributed in the two hands.

The tick of a watch was heard normally. The tongue was broad and flat, and was moist. The teeth were in good condition. The tonsils were not enlarged.

The trachea was in the midline; the thyroid was not palpable; there was a well healed thyroidectomy scar.

There was no general glandular enlargement.

The lungs were clear to percussion and auscultation.

The pulses were equal and synchronous, and were regular in force and rhythm. The rate was 60 per minute.

The heart sounds were clear at the apex and the base. The second aortic sound was loud and "plupping." The blood pressure was 150 systolic and 110 diastolic.

The liver and spleen were not felt. There were no masses in the abdomen.

The phallus and gonads were normal. There was a slight left varicocele. The inguinal glands were slightly larger than normal.

The reflexes were very active. Chvostek's and Trousseau's signs were negative.

There was an extreme degree of clubbed fingers, with enlargement of the hands and wrists. There were a thickening and bowing of the left second metacarpal and

also a thickening of the soft parts around all of the middle phalanges. There was thickening of the wrists. The elbows and shoulders were normal. The feet were approximately normal. There was excessive edema from the top of low shoes to the knees. The skin of this area was brawny and pigmented.

Impression.—The patient probably had slight postoperative myxedema. The interesting feature was the hypertrophic osteo-arthropathy, a possible explanation of which may be found in the alteration of the circulation following a sudden reduction of the metabolic rate.

Laboratory Studies.—The urine was a clear, medium amber; the specific gravity was 1.027; it was acid; it contained no sugar, a trace of albumin, a few hyaline casts, a few epithelial cells and white blood cells, but no red blood cells.

Fig. 4.—Brawny edema of the legs.

A blood count showed: hemoglobin, 91 per cent; red cells, 4,720,000; white cells, 13,650. A differential count showed: polymorphonuclears, 73 per cent; polymorphonuclear eosinophils, 4 per cent; polymorphonuclear basophils, 1 per cent; small lymphocytes, 20 per cent; large lymphocytes, 2 per cent.

Roentgen examination showed that the lungs were clear. The heart and aorta were normal in size. The right border of the heart was 5 cm. from the midline; the left border, 9.5 cm.

The metacarpal bones were short. There were a few periosteal changes in the bones of the hands and the legs; otherwise, the bones were normal.

On Feb. 15, 1929, the basal metabolic rate was —9 per cent (perfect test). The patient weighed 177 pounds, (80.3 Kg.); the pulse rate was 56.

An electrocardiogram showed a rate of 52; the rhythm was sino-auricular; the P-R interval was 0.19 second. The T waves were all upright. There were normal sinus rhythm and sinus bradycardia.

On February 18, chemical analysis of the blood showed: nonprotein nitrogen, 32 mg. per hundred cubic centimeters; calcium, 11.4 mg., and phosphorus, 4 mg.

The patient was requested to enter the hospital for observation and treatment but declined and disappeared from sight until April 9, 1931.

Interval History.—Since the patient was last seen he had worked spasmodically as a tailor's helper, but had not felt well. He had noticed no change in the size or shape of his hands and legs. In January, 1931, he fell, injuring his back and right leg, and he was still shaky and nervous from the fall, and had pain in the left flank.

On April 9, roentgen examination showed marked new bone formation in the bones of the hands and feet.

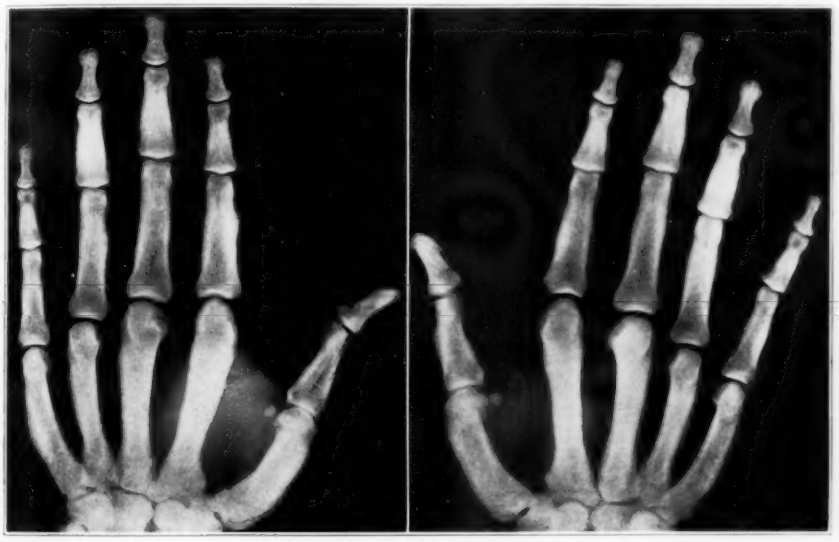

Fig. 5.—Roentgenogram taken two years after subtotal thyroidectomy, showing tufting of the terminal phalanges and marked subperiosteal new bone formation symmetrically distributed in the two hands and underlying the soft tissue swelling seen in the photograph.

On April 14, roentgen examination showed marked periosteal changes in the bones of the hands. The long bones, the head and the spine were normal.

The Wassermann reaction was negative.

The blood pressure was 160 systolic and 120 diastolic. It was the same in the two arms.

Laboratory Studies.—Urinalysis showed a specific gravity of 1.016 for the specimen taken in the morning and 1.026 for the specimen taken in the afternoon; both specimens contained albumin (+) but no sugar. Microscopic examination revealed a few white blood cells and 1 hyaline cast.

The phthalein test gave the following reactions: first hour, 43 per cent; second hour, 12 per cent, totalling 55 per cent. Nonprotein nitrogen was 38 mg. per hundred

cubic centimeters; total proteins, 7.95 mg.; A/G ratio, 63/37; calcium, 10.2 mg. per hundred cubic centimeters; phosphorus, 3.7 mg., and cholesterol, 230 mg.

On April 24, the basal metabolic rate was —20 per cent (perfect test). The pulse rate was 54; the weight was 187 pounds (84.8 Kg.).

On this day, thyroid medication was begun, 1 grain (0.065 Gm.) a day. After eighteen days the patient reported that he felt much better. He had no pain in the back, and the pulse rate was 62. Thyroid extract, 2 grains (0.13 Gm.) a day after fourteen days produced "quivers around the heart."

The capillaries of the nail beds were examined microscopically by Dr. J. Evans, who found an unusual condition. There was a great dilatation of the venous side

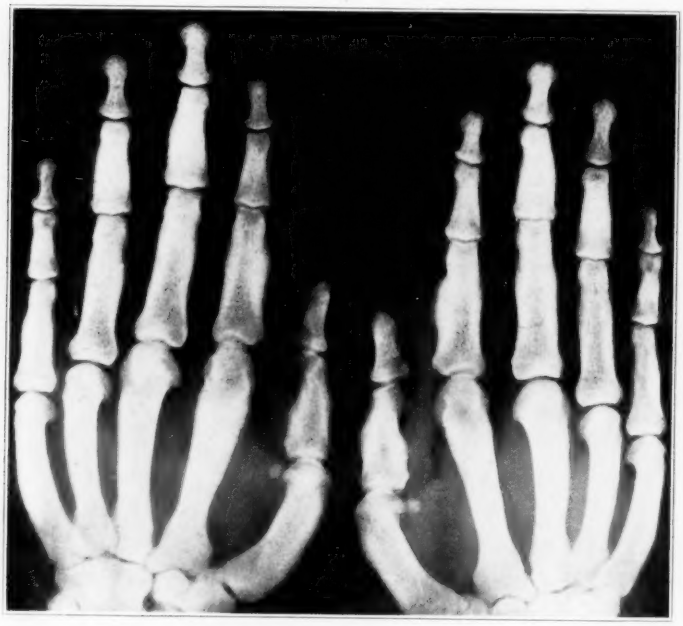

Fig. 6.—Roentgenogram taken four years after subtotal thyroidectomy, showing increase in bony changes.

of the capillaries, and the arterial side showed an extreme degree of tortuosity. The capillary pressure was slightly elevated.[3]

Thyroid extract, 1½ grains (0.097 Gm.) a day for a month, produced very little change, and the patient was annoyed by insomnia, aching around his eyes and great fatigue in the afternoon which required two hours of sleep.

The patient took thyroid steadily from Nov. 22, 1931, to two weeks before this article was written. He felt somewhat better, but there was no noticeable change in the condition of his hands and legs.

3. Hölger, F.: Ueber Akropachie (Trommelschlägelfinger und Osteoarthropathie), Wien. Arch. f. inn. Med. **1**:35, 1920. Hölger said: "Interesting but inconclusive is the finding of normal capillaries in clubbed fingers in vivo in one case."

Summary of Case.—A young colored man of 22 years was admitted to the hospital in November, 1926, suffering from a rather severe form of diffuse goiter with hyperthyroidism, which, judging from the history, had existed for two years. Following the usual treatment and operation, the basal metabolic rate fell from the admission

Fig. 7.—Larger view of roentgenogram taken four years after subtotal thyroidectomy.

level of 59 per cent above normal to 3 per cent below normal, and he gained 26 pounds (11.8 Kg.). After his discharge from the hospital he gained about 30 pounds (13.6 Kg.) more in eight months. At the end of this time he noticed clubbing of the fingers and a change in the swelling of his ankles which, previously transitory, had become constant

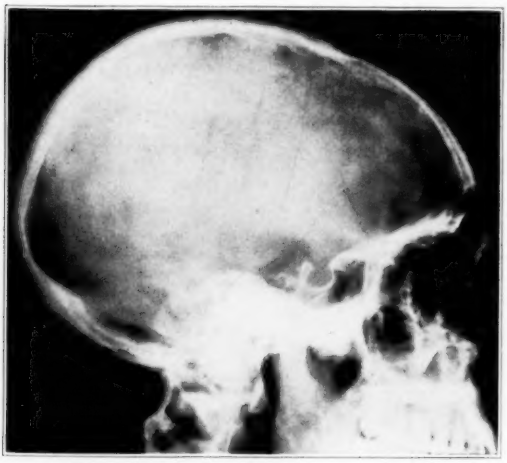

Fig. 8.—Roentgenogram of skull, showing a normal sella turcica and absence of characteristic changes seen in Paget's disease.

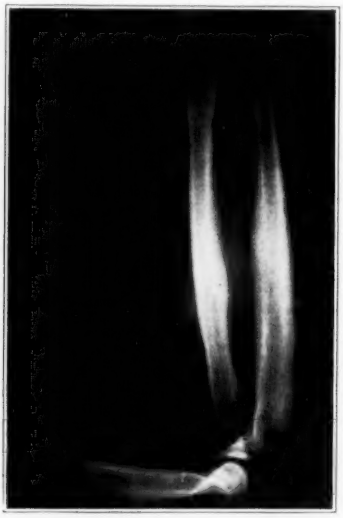

Fig. 9.—New bone formation in long bones of the arms, most marked in the middle of the diaphysis.

and firmer. The conditions increased gradually, but with only slight pain and that only on vigorous movement of the hands. In 1929, the basal metabolic rate was —9 per cent, and x-ray pictures showed laying down of new bone under the periosteum of the bones of the hands and feet and the long bones of the extremities. In April, 1931, the basal metabolic rate was —20 per cent and the new bone formation had become more extensive. A diagnosis of postoperative hypothyroidism with secondary hypertrophic osteo-arthropathy was made, and thyroid replacement therapy was instituted, with definite improvement in the subjective symptoms. No convincing change has been noted in the bones since the patient began to take thyroid, although an apparent thinning of the subperiosteal new bone has been seen at the end of three and a half months.

COMMENT

This is the first reported case of clubbed fingers with subperiosteal new bone formation occurring in association with disease of the thyroid gland. The changes in the bones of the hands are as extensive as any described in the literature, and the swelling of the legs is greater. The new bone is confined to portions of the skeleton which are covered by periosteum and is not seen in the joints. It is greatest in the midportion of the short bones, but involves the entire length of most of the long bones as well. There is also a well marked increase in the tufting of the terminal phalanges of the fingers. Because the swelling of the soft parts in this case occurs so clearly above the bony changes, even including the tufting of the terminal phalanges, it would seem probable that the clubbed fingers which are seen in this condition may represent a soft tissue change different from that of clubbed fingers which occur without any underlying bony change.

Most patients acquire the new bone in thin layers under the periosteum, several layers becoming visible in the x-ray film as time goes on. The case reported, however, shows a piling up of new bone with a fuzzy surface to a thickness of 2 or even 3 mm. This difference might well be due to the rapidity of the process. The swelling of the soft parts in the hand (and presumably elsewhere also) occurs over the bony swelling as though it were part of the same process. One extraordinary feature of the condition, which has been commented on before (Fraenkel [4]), is the symmetry of the process. The same portion of the same bones in the two hands is involved to approximately the same degree. Hitherto this condition has been described as being secondary to suppurative intrathoracic lesions, mediastinal new growths, tumors of the lung, abscess of the liver, pyelonephritis, cirrhosis of the

4. Fraenkel, E.: Ueber allgemeine Periostitis hyperplastica (Osteo-arthropathie hypertrophiante pneumique), Fortschr. a. d. geb. d. Röntgenstrahlen **25**:401, 1918.

liver with jaundice, certain obstructive lesions of the gastro-intestinal tract, possibly syphilis, and, perhaps incorrectly, congenital heart disease. The case reported presents none of these features.

In 1889, von Bamberger [5] reported two cases of bronchiectasis in which clubbing of the fingers and toes and gross changes in the bones of the lower legs developed. He attempted to reproduce the bony changes in rabbits by injecting the patient's sputum into the animals, on the theory that the etiologic factor was a toxin liberated by the suppurative process.

The following year Pierre Marie [6] described a syndrome which he called hypertrophic pulmonary osteo-arthropathy (ostéo-arthropathie hypertrophiante pneumique), consisting of widespread enlargement of the bones and clubbing of the fingers in cases of cardiac and pulmonary disease. He was careful to differentiate this condition from acromegaly, although his best case, seen in the light of further knowledge, undoubtedly combined certain features of acromegaly with hypertrophic pulmonary osteo-arthropathy. Later on much interest was aroused by the constant accompaniment of clubbed fingers (Trommelschlägelfingern) with the bony changes, as this secondary enlargement of the distal phalanges of the fingers and toes had been noted by Hippocrates. Trousseau,[7] after several centuries during which it had been overlooked, described the condition of clubbed fingers accurately and pointed out its association with advanced pulmonary tuberculosis, empyema, emphysema, nervous asthma and organic heart disease.

After the appearance of von Bamberger's article in Germany and Marie's in France, clinicians in many countries reported cases secondary to various diseases, among which were tuberculosis, bronchiectasis, empyema, abscess of the lungs, tumor of the lungs, lymphoblastoma, organic heart disease, syphilis, cirrhosis of the liver with jaundice and amebic hepatitis, with a few apparently spontaneous cases. In 1898, Schmidt [8] collected the literature on the subject. He concluded that clubbed fingers, with the change confined to the soft tissues, represent an early stage of what may or may not further develop into the more advanced and rarer form with bony thickening. He thought that the joints are never involved, and that the greatest swelling occurs in the middle portion of the shaft of the long bones. Most of the bones of the skeleton may show changes, including the clavicle and the ilium.

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5. von Bamberger, E.: Bronchiektasie, Wien. klin. Wchnschr. **2**:*226*, 1889.

6. Marie, Pierre: De l'ostéo-arthropathie hypertrophiante pneumique, Rev. de méd. **10**:1, 1890.

7. Trousseau, Armand: Lectures on Clinical Medicine, translated by John Rose Cormack, Philadelphia, Lindsay & Blakiston, 1868, vol. 3.

8. Schmidt, M. B.: Die allgemeine hyperplastische Periostitis und Ostitis, Ergebn. d. allg. Path. u. path. Anat. **5**:932, 1898.

In this country, Thayer,[9] Janeway,[10] Landis[11] and others have written on the subject, and in 1915, Locke[12] summarized the literature and added five carefully studied cases. He considered the clubbed fingers and bony swelling as part of the same condition and stated that early subperiosteal changes could be demonstrated in all of his cases of clubbed fingers.

In 1917, Fraenkel[4] reported seven additional cases and argued against the earlier impression (agreeing on this point with Schmidt) that the joints and periarticular tissues (cartilage) are commonly involved. None of the cases he studied at autopsy showed any such change, and he conceived the condition to be a form of hyperplastic periostitis which involves characteristically the midbones of the hands and feet and the midportion of the long bones. The underlying old bone may be unchanged or may show thickening or thinning.

A splendid article on the subject was published in 1920 by Högler,[8] from Falta's Clinic in Vienna. He reported five cases, one of which was merely a case of clubbing of the fingers, and he carefully analyzed the case reports from the previous literature. If his conclusions are correct, and it certainly seems that in most respects his points are well taken, some of the ideas on the subject must be readjusted.

In an effort to eliminate the obvious disadvantages of most of the names that have been applied to this condition, such as chronic hypertrophic pulmonary osteo-arthropathy, hyperplastic periostitis, ossifying periostitis, secondary ossifying periostitis, toxic periostitis and toxicogenic osteoperiostitis ossificans, Högler suggested the name acropachy. By this name he avoided pathologic descriptive terms, which are likely to be incorrect (there is no evidence of inflammation of the periosteum, and the joints are rarely involved), and terms suggesting the etiology, which are also likely to be incorrect or inconclusive, and he hinted at a similarity to acromegaly, with which the condition was first confused.

The change in the bone consists of a deposition of new bone between the cortex and the periosteum of the long bones, particularly the lower ends of the bones of the forearms and the lower legs and the metacarpal and metatarsal bones. In extreme cases similar changes have been described in the clavicles, ribs, pelvic bones, scapulae and malar bones, and even in the transverse processes of the vertebrae. The joints are

9. Thayer, W. S.: Hypertrophic Pulmonary Osteo-Arthropathy and Akromegaly, Philadelphia M. J. **2**:955, 1898.

10. Janeway, T. C.: Hypertrophic Osteo-Arthropathy: With Report of Two Cases, Am. J. M. Sc. **126**:563, 1903.

11. Landis, H. R. M.: Hypertrophic Pulmonary Osteoarthropathy with a Report of Two Cases, Pennsylvania M. J. **10**:852, 1907.

12. Locke, E. A.: Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club-Fingers, Arch. Int. Med. **15**:659 (May) 1915.

never involved in the original process, although involvement of the end of the bone may lead to disability in the joint. The underlying bone shows no change except that seen following disuse. Histologically, the cortical part of the bone is little if any changed (Schlagenhaufer [13]). Högler disagreed with Sternberg, who described evidence of inflammation in the periosteum itself. More and more, he said, it looks like a hyperplastic process of the periosteum. This has a true analog in the osteophyte building during pregnancy, but is not a true inflammation.

Often there is swelling of the wrists and ankles, and the swelling of the ankles may even amount to brawny edema.

The condition may be painful or associated with tender points over the affected areas.

Although acropachy usually occurs in patients with clubbed fingers, several cases have been described in which clubbed fingers were not present, and also innumerable cases of clubbed fingers have occurred without any bony changes. For these reasons it appears that this syndrome is quite distinct from that of clubbed fingers, although the two conditions probably are caused by the same variety of underlying morbid process.

On careful analysis, most of the authentic cases were found to occur in patients suffering from some collection of pus in the chest or some form of mediastinal new growth, usually lymphogranuloma. Högler doubted whether any true case has occurred secondary to congenital heart disease without accompanying pulmonary disease. Unilateral involvement of one arm has been described in cases of aneurysm of the subclavian artery and in trauma to the brachial plexus. A number of characteristic cases have been observed following biliary cirrhosis of the liver with jaundice. Finally, a small number of cases with no obvious etiology may be found in the literature.

Högler thinks it interesting that most cases follow a purulent process in the thoracic cavity or a mediastinal growth from which some toxic substance may emanate. In one of the cases of lymphogranuloma with a mass in the mediastinum which he reported, the patient was treated by irradiation of the mediastinal mass. Along with the general clinical improvement, the bony changes, which had been extreme, faded away until they were hardly noticeable in the x-ray films. Högler pointed out that Gerhardt,[14] Liebermann,[15] Ruhle [15] and Hoffmann [16]

13. Schlagenhaufer, F.: Ueber diffuse ossifizierende Periostitis, Ztschr. f. Heilk. **25**:364, 1904.

14. Gerhardt, Carl: Lehrbuch der Auskultation und Percussion, Tübingen, H. Laupp, 1900, p. 26.

15. Liebermann, cited by Högler.[3]

16. Hoffmann, V.: Ein Beitrag zur Kenntnis der Osteo-arthropathie hypertrophiante pneumique, Deutsches Arch. f. klin. Med. **130**:201, 1919.

wished to give chief etiologic importance to congestion, but he said later that congestion plays no important rôle, since cases of heart failure are no longer included as a special group, and since there is another group of cases of high grade acropachy in which stasis in the large and small circulation is entirely precluded.[17] After considering the possible influence of toxins on trophic nerves in the periosteum, the possibility of an irritating substance which perhaps can be generated by malignant tumors, etc., Högler finally concluded that it must be admitted that this hypothesis really is nothing but another way of writing down the important facts which depend on various observations and experimental data.

In 1923, Schirmer [18] published an autopsy report on one of Högler's patients who subsequently died of "lymphoblastoma" or Hodgkin's disease. There existed infantilism with a normally formed but extremely underdeveloped thyroid gland and with a normal hypophysis. He referred to Franchini,[19] who in 1910 reported a case of putrid bronchitis with atrophy of all the endocrine glands and an infantile habitus. Braun [20] found an adenoma or some other lesion of the hypophysis in three or four cases of this condition, and suggested that the bony changes are caused by a dysfunction of the pituitary gland.

The case reported in this article presents several interesting features. In the first place, it developed shortly after the condition had changed quite suddenly from a condition of hyperthyroidism to one of hypothyroidism by iodine medication followed by subtotal thyroidectomy. Careful search before operation and on many occasions after operation, over a period of five years, has failed to reveal any other disease process either in the thoracic cavity or elsewhere in the body. One is forced, then, to conclude that in this case the changes were in some way produced by a rapid alteration in the patient's endocrine balance. No such changes have been observed in exophthalmic goiter or in myxedema. Long-standing cases of hyperthyroidism do exhibit generalized osteoporosis, and conversely myxedema tends to produce a widespread increased density of the bone, but without change in the size of the bone and without new bone formation. The changes of the bones in parathyroid disease are striking, but, again, they differ mark-

17. I should like to suggest that a slowing of the entire blood flow may occur without local evidence of congestion and yet still have its effect on such tissues as the periosteum, even if the generally accepted connection between congenital heart disease and acropachy is incorrect.

18. Schirmer, Oskar: Beitrag zur Kenntnis der Akropachie (Osteoarthopathie hypertrophiante pneumique), Wien. Arch. f. inn. Med. **5**:345, 1923.

19. Franchini, G.: Sull'osteoartropatia ipertrofica pneumica di Marie: Studio clinico de anatomo-pathologico, Riv. crit. di. clin. med. **11**:745, 1910.

20. Braun, H.: Ueber Trommelschlägelfinger, Med. Klin. **14**:1, 1918.

edly from those in the case presented by involving the original bony structure in a condition known as osteitis fibrosa cystica. No indication of parathyroid dysfunction in my case could be brought to light, and the determinations of the blood calcium and phosphorus were always normal. That one or more of the other glands of internal secretion were altered functionally by the operation on the thyroid gland seems likely, but I am unable to connect such changes with the development of new bone. The thymus gland is frequently found enlarged in cases of exophthalmic goiter. That the thymus should assume such proportions as to be considered a mediastinal tumor which might produce pressure and yet not be visible in the x-ray picture of the chest seems doubtful, but barely possible. Pressure symptoms in an adult from an enlarged thymus are rarely if ever seen. No involvement of the pituitary gland was demonstrable by roentgen examination of the sella turcica, by determination of the visual fields or by sugar tolerance tests. It is inferred that a change in the functions of the pituitary gland probably accompanies changes in the function of the thyroid gland, but in the case reported a skeletal deformity quite different from acromegaly or gigantism was encountered.

In the roentgenograms of the pelvic bones certain areas of rarefaction faintly suggested Paget's disease, but examination of the other bones, particularly the skull and the spine, did not support this idea, and changes like those seen in the bones of the hands in my case have not been described in Paget's disease.

One might quite properly, it seems to me, place some importance on the sudden change in blood flow which is known to take place in any case when a hyperthyroid condition is abruptly converted into one of hypothyroidism. Blumgart [21] and others have shown that in hyperthyroidism the blood volume is greater than normal, the minute output of the heart is more than normal, and the blood flow is faster than normal. They have also shown that in hypothyroidism the blood volume, the minute output of the heart and the rate of blood flow are reduced below normal. It would appear, then, that in a young adult this sudden slowing of the circulation has for some reason been accompanied by the remarkable abnormality described. The perfect bilateral symmetry of the lesion requires an explanation. What condition, one must ask oneself, might affect the bone or periosteum of the two arms in such an irregular but identical manner? Would not a circulating toxin call forth a similar response in all of the proximal phalangeal bones instead of selecting the mesial surface of each proximal phalangeal bone on

21. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIII. The Circulatory Response to Thyrotoxicosis, J. Clin. Investigation **9**:69, 1930; XIV. The Circulation in Myxedema with a Comparison of Blood Flow in Myxedema and Thyrotoxicosis, ibid. **9**:91, 1930.

which to concentrate its attentions? Alteration of the circulation, on the other hand, might easily affect one finger, for instance, the index finger, before the others, and this, of course, would be true for both sides alike. In my case, as in those reported by Högler, a persistent, edema-like swelling of the lower extremities is strong evidence in favor of local congestion. One is led to wonder whether the common factor in all of these cases may not be some change in the circulation. Such a change occurs in cases of jaundice with bradycardia and might also occur if a fraction of the lung substance ceased to act properly in its function of aerating the blood. Mechanical pressure from a mediastinal mass does interfere with the blood flow in the great vessels, and the disappearance of the bone changes in such a case following deep roentgen therapy to the mediastinum may be accounted for by the removal of such pressure. It would seem that the circulatory change must be abrupt, and that its effect is most striking when it occurs in patients whose osseous system is still in the process of adolescent growth.

It is important to point out the obvious objections to considering circulating toxins the cause of acropachy. Why, for instance, should an abscess of the lungs produce such a toxin and abscesses elsewhere in the body not produce it? Why should it occur in its most advanced form with Hodgkin's disease which involves the glands of the mediastinum, and not occur with Hodgkin's disease confined to glands elsewhere in the body? Why should it occur with carcinoma of the bronchus and not with carcinoma in other parts of the body? Why should this toxin be liberated by pulmonary tuberculosis and not by tuberculosis of other organs?

As may be inferred, I am not in favor of the theory of a circulating toxin. In all honesty, however, I must confess self-evident objections to the theory of an altered blood flow. Why does one not see acropachy in the many cases of unilateral femoral thrombophlebitis? So far as I know, subperiosteal new bone may occur in these cases without ever having been noticed. If an insufficient oxygen supply is an important feature, why has acropachy not been found in long-standing cases of severe anemia? It may be, I think, that the tissue adjustment to anemia is gradual, whereas in acropachy time for adjustment is lacking.

SUMMARY

I have presented the case of a young colored man in whom diffuse goiter with hyperthyroidism developed for which subtotal thyroidectomy was performed. Eight months later he noticed clubbing of the fingers and brawny swelling of the legs, and when examined two years later was found to have an extreme degree of acropachy. A careful exami-

nation made at the time of operation and repeated on two further occasions, two and again four years after operation, failed to reveal other disease or lesion of the heart or lungs. I found no mention of similar cases in the literature, but I have discussed the important articles on acropachy as it occurs in various other conditions. Nothing is known concerning the mechanism of the bony change in this syndrome.

The new and unusual case I have reported adds strong evidence of the importance of altered blood flow in the production of subperiosteal new bone formation. The only conclusion I am able to reach, after contemplating the many factors involved in cases of acropachy, is that an altered blood flow offers itself as the most plausible common etiologic factor.

RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND NITROGEN METABOLISM

II. IN LEUKEMIA

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In a previous communication [1] we presented evidence of a decrease in the total oxygen consumption during induced remissions in pernicious anemia. A relationship between the oxygen consumption and nitrogenous metabolism was discussed. The data in the present report were obtained by metabolic studies in leukemia, another disease group in which there is an altered rate of oxygen consumption without a recognized disturbance in thyroid function. We again wish to stress the relationship between oxygen consumption and nitrogenous metabolism.

The published reports of metabolic studies in leukemia contain much important information, but the established facts have not been satisfactorily correlated. We do not propose to present an exhaustive review of the literature but rather to mention only those observations which bear directly on our present problems.

REVIEW OF LITERATURE

It is quite universally agreed that the rate of oxygen consumption is increased, sometime during the course, in all forms of leukemia. Grafe,[2] though not the first [3] to observe the increased basal metabolic rate in leukemia, has been the most persistent contributor to the literature on the subject and has advanced many of the prevalent theories

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1. Baldridge, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: I. In Pernicious Anemia, J. Clin. Investigation **10**:529, 1931.

2. (*a*) Grafe, E.: Die pathologische Physiologie des Gesamtstoff- und Kraftwechsels bei der Ernährung des Menschen, Ergebn. d. Physiol. **21**:464; 1923; (*b*) Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursache, Deutsches Arch. f. klin. Med. **102**:406, 1911; (*c*) Stoffwechseluntersuchungen bei Milz- und Lebererkrankungen, Deutsches Arch. f. klin. Med. **139**:354, 1922; (*d*) Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 5, p. 267.

3. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl. klin. Wchnschr. **30**:417, 1893.

as to the genesis of the increased utilization of oxygen in this disease. It has been suggested that the oxygen consumption in afebrile leukemia, which is often 50 per cent above the normal and may reach 100 per cent above, can be explained as follows: (1) increased pulse and respiratory rates; (2) increased utilization of oxygen by extra leukocytes, especially the abundant and very active young forms, both in the blood and in the tissues; (3) increased activity and extent of the hematopoietic tissue; (4) anemia (in which an increased amount of oxygen is used by young erythrocytes), and (5) possibly toxic factors.

The possibility that the spleen has an endocrine function and thus plays a rôle in general metabolism has been suggested by the Asher school. Since both the spleen and the metabolism are abnormal in leukemia, suggestions as to a cause and effect relationship have naturally appeared in the literature. The discussions, which have been summarized by Stüber,[4] are very vague and unconvincing. Stüber also takes the unique position of attributing part of the increased metabolism in leukemia to an increased imperceptible loss of water.

Murphy, Means and Aub[5] found that direct and indirect calorimetry agreed in a case of lymphatic leukemia, thus showing that no measurable heat was derived from permanently anaerobic reactions. Isaacs[6] suggested that nuclear destruction might be related to the increased oxygen consumption in blood dyscrasias because of the increased uric acid excretion, which is common to pernicious anemia, leukemia and polycythemia vera. Riddle and Sturgis[7] as well as Krantz and Riddle[8] found an occasional rise in oxygen consumption after roentgen therapy, and suggested the possibility that blood destruction might also play a rôle in increasing the oxygen consumption in leukemia. Both groups of workers appear to have been more impressed, as Gunderson[9] had been, with a fairly good correlation between the number of circulating immature cells and the total metabolism.

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4. Stuber, K.: Ueber den Gaswechsel und die spezifisch-dynamische Eiweisswirkung bei Leukämien und Pseudoleukämien, Ztschr. f. klin. Med. **111**:214, 1929.

5. Murphy, J. B.; Means, J. H., and Aub, J. C.: The Effect of Roentgen-Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, Arch. Int. Med. **19**:890 (May) 1917.

6. Isaacs, R.: Pathologic Physiology of Polycythemia Vera, Arch. Int. Med. **31**:289 (Feb.) 1923.

7. Riddle, M. C., and Sturgis, C. C.: Basal Metabolism in Chronic Myelogenous Leukemia, Arch. Int. Med. **39**:255 (Feb.) 1927.

8. Krantz, C. I., and Riddle, M. C.: The Basal Metabolism in Chronic Lymphatic Leukemia, Am. J. M. Sc. **175**:229, 1928.

9. Gunderson, A. H.: The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, Boston M. & S. J. **185**:785, 1921.

A considerable amount of information has accumulated from experimental work bearing directly or indirectly on the various factors which have been thought to contribute to the increased gaseous metabolism in leukemia. We believe that a critical review of these factors in an attempt to evaluate their importance would be worth while even though it is readily admitted that in vitro experiments of the Warburg type may not give exact information as to gaseous metabolism in vivo.

THE INFLUENCE OF CARDIAC AND RESPIRATORY RATES

It is well known that the pulse rate usually increases as a *result* of increased oxygen consumption. It is also known that the rate of absorption of oxygen in the lungs is independent of the respiratory rate.[10] Changes in the cardiac and respiratory rates within reasonable limits, therefore, will influence the oxygen consumption only by virtue of changes in the muscular effort involved. Riddle and Sturgis [7] found that in myelogenous leukemia the pulse rate increased about 7 per cent for each 10 per cent increase in the basal metabolic rate. In our own patients with chronic leukemia the basal respiratory rate was rarely found to be above 18 per minute. Grafe has estimated that if both the cardiac and respiratory rates were doubled, the total metabolism would thereby be increased 8 per cent. However, we have never found either the cardiac or the respiratory rate to be doubled in patients with afebrile leukemia under basal conditions. Starling and Visscher [11] found that an increase in the heart rate of about 35 per cent caused an increase of about 20 per cent in the oxygen consumed by the heart-lung preparation when the diastolic volume of the heart was kept constant. The same investigators [12] also found that the oxygen consumption of the heart-lung preparation was about 5 per cent of the total for the anesthetized animal. It should be stated, however, that the actual oxygen consumption of the heart-lung preparation of Starling and Visscher was about 10 per cent of the calculated basal requirement for dogs weighing from 8 to 9 Kg. (This was the average weight of dogs used by these investigators.) With the pulse rate changes observed by Riddle and Sturgis, it can be seen that in the average leukemic patient with a basal metabolic rate 50 per cent above normal there would be a 35 per cent increase in pulse rate. The amount of oxygen used by extra heart beats per se would therefore be approximately from 1 to 2

10. Pflüger, E., quoted by Lusk, G.: The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1928, p. 32.

11. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**:243, 1927.

12. Visscher, M. B.: Personal communication.

per cent of the total oxygen consumption if relationships in the dog can be transferred to man. The extra muscular effort occasioned by the slight increase in respiratory rate should be of even less significance.

THE INFLUENCE OF EXTRA LEUKOCYTES

An increase in the total leukocytes of the body might be expected to increase the basal metabolic rate since their presence would increase the surface area but slightly, and since they replace structures of relatively low metabolism such as fat, connective tissue, blood plasma and erythrocytes. All recent investigators agree, however, that there is no consistent or linear relationship between the number of extra leukocytes in the blood and the total oxygen consumption. We have made similar observations as well as an attempt to correlate the size of the spleen and liver with the height of metabolism but always with inconsistent results. Such a parallelism would be mandatory if the respiration of these added leukocytes were the principal cause of the increased metabolism in leukemia. Furthermore, the apparent correlation between the number of immature leukocytes and the total metabolism as suggested by Gunderson,[9] by Riddle and Sturgis[7] and by Krantz and Riddle[8] cannot be due directly to the respiration of these young cells. Glover, Daland and Schmitz[13] and Daland and Isaacs[14] concluded that young leukocytes consume less oxygen than adult cells of the same series, while Soffer and Wintrobe[15] concluded that if allowance were made for concentration the oxygen consumption of adult and young leukocytes would be about the same. There are no results to substantiate the claim of Grafe that "the active young forms" use more oxygen than adult leukocytes. Since the literature contains many studies on the oxygen consumption of leukemic blood, it is easy to calculate the amount of oxygen used by leukemic blood as contrasted with the normal. Considering that the blood constitutes 7 per cent of the body weight[16] and using an average of the results obtained by Glover, Daland and Schmitz for the respiration of leukemic blood, it appears that the blood of leukemic patients may use an average of 3 per cent of the normal total oxygen consumption. The gaseous metabolism of leukemic blood as determined by Glover, Daland and

13. Glover, E. C.; Daland, G. A., and Schmitz, H. L.: The Metabolism of Normal and Leukemic Leukocytes, Arch. Int. Med. **46**:46 (July) 1930.

14. Daland, G. A., and Isaacs, R.: Cell Respiration Studies, J. Exper. Med. **46**:53, 1927.

15. Soffer, L. J., and Wintrobe, M. M.: The Metabolism of Leukocytes from Normal and Leukemic Blood, J. Clin. Investigation **11**:661, 1932.

16. Chang, H. C., and Harrop, G. A., Jr.: The Determination of the Circulating Blood Volume with Carbon Monoxide, J. Clin. Investigation **5**:393, 1928.

Schmitz gave results of the same order of magnitude as those obtained by Daland and Isaacs,[14] by Hastings and Davis,[17] and by Barron and Harrop.[18] Grafe, in earlier work, obtained much higher figures from which he calculated that the blood might use as much as 10 per cent of the total oxygen consumed.[2b] Let us assume that the leukocytes which are extravascular but which are not involved in cell division or metaplasia (so-called infiltrated leukocytes) are twice as numerous and have the same respiratory activity as the circulating leukocytes. If the presence of such leukocytes did not affect the calculated surface area of the patient, it can be seen that they might use 6 per cent of the total normal oxygen consumption. This estimation is probably extremely generous since the in vitro oxygen consumption of leukocytes is much lower when they are grouped in large masses than when they are well diluted in plasma.[19]

INFLUENCE OF INCREASED EXTENT AND ACTIVITY OF THE HEMATOPOIETIC BONE MARROW

The extent of leukopoietic tissue in all types of leukemia is greatly increased both because of replacement of fat in the bone marrow and because of metaplasia outside the normal hematopoietic tissue. Metaplasia will be discussed with "activity," however, so that for the moment, we are concerned only with the extent of the bone marrow. In leukemia it is common to find the normal hematopoietic marrow of the flat bones more cellular than usual and in addition a partial or complete replacement of the fatty marrow of long bones by hematopoietic tissue. In addition to the increase in extent of the bone marrow, erythroblastic elements are often partially replaced by leukoblastic elements, which latter cells are usually considered to be more actively respiring than the former. However, it should be remembered that leukoblasts use no more or even less oxygen than leukocytes of the corresponding series, and that the possible capacity of the bone marrow is limited (from 1,600 to 4,000 cc.).[20] No exhaustive studies as to the relative numbers of cells in the normal and in the leukemic bone marrow are available at present, but it is estimated by Isaacs[21] that the nucleated cells of the sternal marrow cannot be increased more than threefold. Let us guess for the present that there may be six times as many cells

17. Hastings, A. B., and Davis, J. E.: Personal communication.

18. Barron, E. S. G., and Harrop, G. A., Jr.: Studies on Cell Metabolism: Metabolism of Leukocytes, J. Biol. Chem. **74**:89, 1929.

19. Soffer and Wintrobe.[15] Hastings and Davis.[17] Barron and Harrop.[18]

20. Schilling, V.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 6, part 2, p. 748.

21. Isaacs, R.: Personal communication.

in the leukemic bone marrow as in the normal. Breza [22] determined the metabolism of the bone marrow of rabbits and guinea-pigs by the Warburg technic. She calculated that the whole hematopoietic bone marrow used 1.5 per cent of the total oxygen consumed by the animals in basal condition, whereas the red bone marrow constituted 2 per cent of the body weight. The same investigator obtained a single reading on human bone marrow which was considerably higher but which needs confirmation. It is hard to understand how an increase in the amount of a tissue the oxygen consumption of which per unit of weight is below the average for the whole body could greatly increase total metabolism even though it replaced structures having a still lower respiratory rate. If the figures cited can be accepted as approximately correct, it becomes obvious that an increase in the extent of the bone marrow would be relatively unimportant in its influence on total oxygen consumption, especially if the oxygen consumption of bone marrow cells is inversely proportional to the concentration [15] as is the case in blood.

The effect on total metabolism of increased activity of blood-forming tissue must be approached from several different angles since the effect of this function alone as separate from other body functions has not been studied. It is essential that we first analyze the meaning of "activity of blood-forming tissue" so far as this is possible. Active hematopoiesis has not been demonstrated to involve any type of work comparable to that of a contracting muscle or a secreting gland. Activity seems to consist only in cell division so far as the true hematopoietic tissue is concerned. The activity of the reticulo-endothelial cells of the bone marrow in the disintegration of broken down erythrocytes is not especially abnormal in leukemia, as judged by the amount of ingested hemosiderin. Furthermore, the latter function has apparently not been considered by those who feel that activity of the bone marrow is an important cause for increased gaseous metabolism in leukemia. We may therefore turn our attention to the amount of energy consumed in cell division.

Loeb [23] showed that in obligatory aerobic eggs, cell division stopped when oxygen was removed from the system. This finding led Zuntz, Liebig, Pflüger and others to suppose that potential energy was stored during growth. However, Warburg [24] was able to show that cell

22. Breza, J.: Studien über Knockenmarksatmung, Arch. f. exper. Path. u. Pharmakol. **117**:240, 1926.

23. Loeb, J.: Die Chemische Entwicklungserregung des tierischen Eies, Berlin, Julius Springer, 1909.

24. Warburg, O.: Ueber Beeinflussung der Sauerstoffatmung, Ztschr. f. physiol. Chem. **70**:413, 1911.

division could be stopped in sea urchin eggs by the addition of 0.01 per cent phenylurethane, a procedure which did not appreciably affect the rate of oxygen consumption. Further, Meyerhof [25] could find no trace of heat liberated on the sudden killing of large numbers of bird erythrocytes. Nor could he demonstrate any extra heat production when growth was stopped and the oxygen consumption maintained at the same rate. Brown,[26] however, found that yeast while fermenting a given amount of sugar produced about 8 per cent less heat under aerobic than anaerobic conditions. Growth occurred under the former conditions and not under the latter. He therefore assumed that the difference in generated heat represented the energy of cell division and growth. He did not, however, prove the presence of stored energy in the yeast. Whitaker [27] recently demonstrated that fertilization and cell division are accompanied by an increase in oxygen consumption in the case of some eggs, while in others a marked decrease in the oxygen up-take is observed. It should be noted that fertilization may in some instances institute catabolic changes which are not present in the mitotic division of hematopoiesis. Except for the observations of Brown, the evidence indicates that nitrogenous substances may be extracted from the surrounding medium and incorporated into cell protoplasm without the use of more oxygen than is required for the life of the cells concerned. Also, the morphologic change of cell division with the formation of new living membranes can be accomplished without the use of a measurable amount of extra oxygen. Indeed, if these conditions did not obtain it would be very difficult to explain the findings of Breza, i. e., that the bone marrow uses less oxygen per unit of fat-free dry weight than most other organs. During adult life true cell division is obviously more rapid in hematopoietic tissue than in any other bodily structure.

Not only is it true that bone marrow "activity" is not responsible for a large oxygen consumption, but when rapid cell formation is separated from an equally rapid cell destruction, the former is actually accompanied by a decrease in the basal metabolic rate. In a previous communication we presented evidence of a decrease in total oxygen consumption during the rapid erythropoiesis of induced remissions in pernicious anemia. As yet unpublished results show a similar drop in the oxygen consumption of dogs during recovery from acute hemorrhagic anemia. This decrease in oxygen consumption occurs during a

25. Meyerhof, O.: Chemical Dynamics of Life Phenomena, Philadelphia, J. B. Lippincott, 1924, p. 87.

26. Brown, H.: Some Studies on Yeast, Ann. Bot. **28**:197, 1914.

27. Whitaker, D. M.: The Oxygen Consumption of Fertilized and Unfertilized Eggs, J. Gen. Physiol. **15**:167, 183 and 191, 1931.

positive nitrogen balance only if the urinary nitrogen is decreased and may be related to the fact that protein which is deposited exerts no specific dynamic effect.[28] The oxygen consumption was determined during the postabsorptive period in all instances, however, so that the decrease in gaseous metabolism was more likely due to the general lowering of protein catabolism during the periods of blood regeneration. It should be noted in this connection that the intact mammal probably differs in at least one important respect from unicellular organisms. Amino-acids once absorbed into the mammalian body must be either deposited, metabolized or rarely excreted in the urine. Therefore, failure to store protein makes a temporary increase in metabolism mandatory, barring excretion, and an environment of abnormally low temperature. The cell membrane of unicellular organisms governs the intake of nitrogenous substance so that such substances probably cannot be forced on unicellular organisms in any way comparable to that seen in the intact mammalian body. Regardless of interpretation, the fact remains that increased activity of the bone marrow where it can be separated from an equally rapid cell destruction has, in our hands, shown a decrease rather than an increase in the total oxygen consumption. The objection might be raised that in leukemia the bone marrow is overactive in the production of leukocytes, while in pernicious and hemorrhagic anemias erythrocytes are being produced. It should be remembered in this connection that the progenitors of both cell types are nucleated, and cell production in both instances is by mitotic division. Furthermore, the decrease in oxygen consumption appears to be roughly proportional to the degree of nitrogen retention. It is therefore apparent that the greater the number of active hematopoietic cells in the body the greater the rate of cell division and the greater the temporary nitrogen storage. If cell destruction could be stopped, the foregoing process should lead to a definite saving of oxygen of sufficient magnitude to offset easily the oxygen requirements of the increased number of preformed cells.

INFLUENCE OF THE ANEMIA OF LEUKEMIA ON THE TOTAL OXYGEN CONSUMPTION

It is perhaps noteworthy that Riddle and Sturgis [7] found no parallelism between the degree of anemia and the increase in metabolism in myelogenous leukemia, while Krantz and Riddle [8] noted such a relationship in the lymphatic type. The anemia of leukemia is of the

28. Rubner, M., quoted by Lusk, G.: The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1928, p. 297. Hoobler, B. R.: The Protein Need of Infants; Being Metabolism Studies of a Two Months' Old Infant Fed with Varying Proportions of Cow's Milk Protein, Am. J. Dis. Child. **10**:153 (Sept.) 1915.

myelophthisic type, and immature erythrocytes and even nucleated forms are quite common in the circulating blood. Erythrocytes containing a reticulum or showing diffuse basophilia have been shown to have a much greater oxygen consumption than normal adult erythrocytes. Warburg,[29] Harrop[30] and Wright[31] all agree on this point, and all agree that the percentage difference is very great. Warburg found that the erythrocytes of young rabbits, in which evidence of youth is more abundant than in human leukemia, may use thirty times as much oxygen as adult human erythrocytes. It must be remembered, however, that the gaseous metabolism of normal human erythrocytes is extremely low. In spite of such a profound percentage increase, the difference between the total oxygen consumption of the normal erythrocytes of the body and a similar number of immature erythrocytes from young rabbits would be sufficient to raise the basal metabolic rate only 0.8 per cent. The total oxygen consumption is within a wide range independent of the amount of circulating hemoglobin. Increased erythropoiesis would lower the oxygen consumption. Increased destruction of erythrocytes might increase the metabolism, but evidence for the presence of this process is certainly not a marked feature in leukemia.

THE INFLUENCE OF TOXIC FACTORS

Grafe[2c] observed a patient with aleukemic myelosis in whom the basal metabolic rate was 29 per cent above normal. He considered that the aforementioned factors were insufficient to account for this increase in oxygen consumption since one factor which he considered to be of great importance, i. e., increase in circulating leukocytes, was entirely absent. He therefore suggested the possibility of some "toxic" factor which increased metabolism. In later publications, however, he decided that it was not necessary to assume the presence of toxic factors.[2d] So far as we are aware, no specific toxic substance has been isolated in leukemia, much less a specific metabolism stimulating substance. If the intermediary products of increased or aberrant protein catabolism can be considered toxic, we would then agree to the presence of a toxic factor. In the absence of any tangible evidence favoring a specific toxic factor, it seems futile and unnecessary to theorize.

The following is a summary of the calculated effects of previously mentioned factors which have been suggested to explain the increased

29. Warburg, O.: Zur Biologie der roten Blutzellen, Ztschr. f. physiol. Chem. **59**:112, 1909.

30. Harrop, G. A., Jr.: The Oxygen Consumption of Human Erythrocytes, Arch. Int. Med. **23**:745 (June) 1919.

31. Wright, G. P.: Factors Influencing Respiration of Erythrocytes; Mammalian Reticulocytes, J. Gen. Physiol. **14**:201, 1930.

gaseous metabolism in leukemia. The calculations are based on the Aub-Du Bois standard for a man, aged 50; height, 150 cm., and weight, 70 Kg. The blood volume is computed according to average figures, i. e., 7 per cent of the body weight and the specific gravity of the blood is assumed to be 1.060. The patient is further assumed to have leukemia with a basal metabolic rate 50 per cent above normal and a 35 per cent increase in pulse rate.

1. Increased cardiac rate—plus 1 to 2, per cent
2. Increased respiratory rate—plus 0 to 1 per cent
3. Increased circulating leukocytes—plus 3 per cent
4. Increased "infiltrated" leukocytes—plus 6 per cent
5. Increased extent of hematopoietic tissue—plus 6 to 9 per cent
6. Increased activity of hematopoietic tissue—minus 10 to 25 per cent
7. Increased respiration of young erythrocytes—plus 0.8 per cent

We cannot, of course, claim a high degree of accuracy for these calculations. They include numerous assumptions, but we have tried to make our assumptions generous. Even though we assume errors of great magnitude in transferring the results of in vitro experiments to conditions in vivo, it is still apparent that the algebraic sum of the effects of factors considered here is entirely inadequate to account for the enormous increases in oxygen consumption which are commonly found in leukemia.

It therefore behooves us to look elsewhere for a factor or factors which might better explain the observed changes in oxygen consumption in leukemia as well as in other blood dyscrasias. The necessity for a more adequate explanation of the altered gaseous metabolism in leukemia is also apparent on the basis of clinical observations. Patients with widespread leukemia fairly frequently have a basal metabolic rate below the accepted normal average. Also, patients with pernicious anemia may have basal rates in the lower ranges of normal at a time when the entire bone marrow is filled by closely packed cells, many of which are nucleated. For the present we choose to ignore such intangible possibilities as a toxic factor and an altered metabolic function of the spleen. We have turned our attention to the obvious increase in protein catabolism which exists in leukemia and have attempted to separate the effects of this process from those of concomitant and equally rapid anabolic processes.

METHODS AND RESULTS

The data presented in this communication were obtained by eight studies on six patients with leukemic myelosis and by two periods of

study on a patient with lymphocytic lymphoma with leukemia (lymphatic leukemia). In six instances the observations included daily basal metabolic rates (Haldone-Tissot), nitrogen balances with nitrogen partitions and phosphorus balances. Control periods immediately preceded and were continuous with the periods following irradiation. On three occasions hourly determinations of the basal metabolic rate were made during a control day, and immediately after irradiation. The remaining observation includes daily studies of the nitrogen balance and oxygen consumption before and after the surgical removal of about 500 Gms. of lymphoid tissue. The diets were low in purine but were not constant

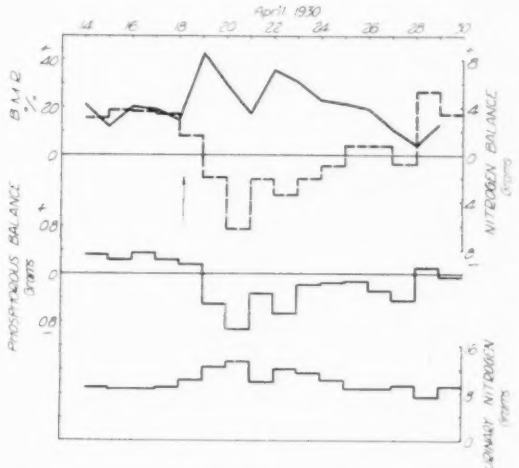


Chart 1.—Curves obtained during metabolic study in case 1. The arrow indicates irradiation. In charts 1 to 7, the solid line indicates the basal metabolic rate; the broken line, the nitrogen balance.

owing to variations in appetite following roentgen treatment. The results are shown in the accompanying charts and tables.

Case 1.—E. M., a white man, aged 31, during the course of a rather trivial infection in the thigh in 1921 had a leukocyte count of 48,000 per cubic millimeter but differential studies were not made at that time. Leukemic myelosis was diagnosed in 1927, at which time the leukocytes numbered 640,000 per cubic millimeter. A total of thirty-one roentgen treatments were given during the three year period preceding our observations, which were begun on April 14, 1930; on April 18, a single dose (600 roentgens as measured in air) was given equally divided between the ventral and dorsal aspects of the splenic area. The spleen decreased about 4 cm. in its long diameter and about 6 cm. in its transverse diameter during the succeeding twelve days.

TABLE 1.—*Data in Case 1*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	98.0	64	12	0.703	+21.0	2,696	0.556	0.234	6.874	0.592	8.958	5.206	+3.272	3,800,000	57,600	+0.349
2	98.8	72	14	0.829	+13.0	2,774	0.679	0.309	5.470	0.542	8.830		+3.848	3,400,000	73,000	+0.246
3	98.4	72	12	0.780	+20.2	2,774	0.526	0.223	6.745	0.459	8.889		+3.788	3,950,000	81,500	+0.367
4	98.4	68	14	0.772	+19.1	2,774	0.518	0.190	6.369	0.485	9.139		+3.538	3,240,000	70,800	+0.244
5*	99.0	68	12	0.780	+14.9	2,698	0.509	0.276	7.613	0.546	10.462	5.054	+1.740	.....	.....	+0.171
6	98.2	72	16	0.709	+43.2	2,198	0.553	0.334	7.412	0.517	12.633		−1.991	.....	.....	−0.501
7	98.0	72	16	0.745	+29.6	2,052	0.536	0.357	9.037	0.825	13.345		−6.253	.....	.....	−0.938
8	98.0	72	14	0.778	+17.7	2,330	0.389	0.281	6.333	0.488	9.925		−2.038	.....	.....	−0.333
9	97.4	64	14	0.739	+35.9	2,358	0.634	0.290	10.154	0.934	12.228		−3.457	2,800,000	31,800	−0.678
10	97.8	64	16	0.838	+31.1	2,540	0.554	0.271	8.733	0.821	11.338		−2.056	3,050,000	29,500	−0.191
11	98.0	64	12	0.745	+23.2	2,617	0.478	0.246	7.070	0.714	10.283	6.004	−0.813	3,400,000	22,000	−0.142
12	98.0	64	12	0.826	+21.5	2,617	0.492	0.238	6.449	0.615	8.708		+0.761	3,100,000	15,400	−0.137
13	98.0	60	16	0.749	+19.2	2,586	0.486	0.272	6.618	0.643	8.727		+0.712	3,600,000	14,400	−0.291
14	97.2	60	12	0.786	+11.7	2,543	0.515	0.353	6.579	0.618	9.234		−0.836	3,230,000	12,100	−0.456
15	97.2	60	12	0.851	+ 4.0	2,774	0.438	0.219	6.083	0.576	7.405		+5.474	3,450,000	17,600	+0.122
16	97.0	64	16	0.782	+12.4	2,774	0.481	0.244	7.289	0.523	9.261		+3.617	3,400,000	15,900	−0.061

* Roentgen therapy (600 roentgens) following determination of the basal metabolic rate. Irradiation was followed by a rather prolonged increase in the urinary nitrogen with only a moderate decrease in the caloric intake. The oxygen consumption reflected the endogenous nitrogen catabolism rather closely. The lack of correlation between changes in the oxygen consumption and changes in the temperature and the pulse and respiratory rates should be noted in all cases.

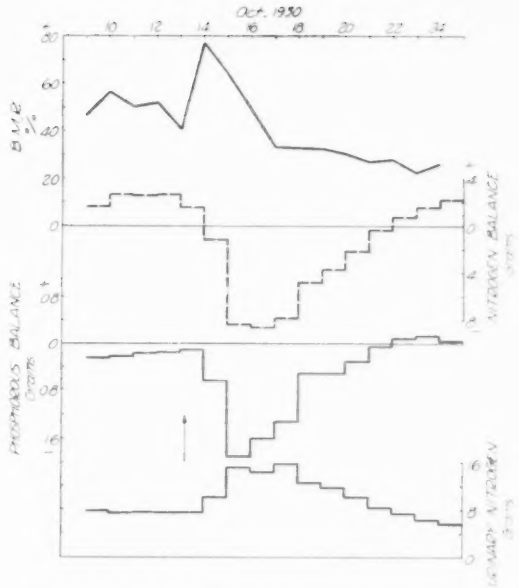


Chart 2.—Curves obtained during metabolic study in case 2. The arrow indicates irradiation.

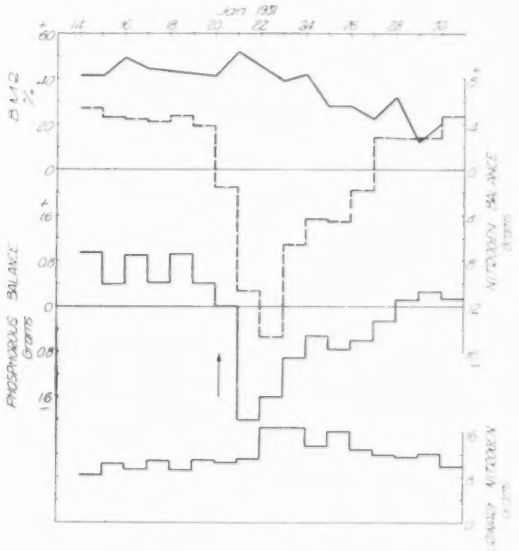


Chart 3.—Curves obtained during metabolic study in case 3. The arrow indicates irradiation.

TABLE 2.—*Data in Case 2*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	99.4	74	16	0.730	+45.8	2,330	0.344	0.160	6.146	0.381	7.964	3.089	+1.786	2,940,000	407,000	−0.366
2	98.8	76	16	0.713	+56.2	2,649	0.333	0.171	5.610	0.349	7.448		+2.702	3,120,000	454,000	−0.209
3	98.4	74	18	0.748	+50.1	2,649	0.355	0.182	5.561	0.306	7.512		+2,638	2,980,000	411,000	−0.159
4	98.6	72	16	0.755	+52.0	2,649	0.374	0.181	5.106	0.319	7.437		+2.712	3,150,000	432,000	−0.152
5*	99.0	72	16	0.748	+41.3	2,340	0.357	0.204	5.708	0.423	7.665	4.270	+1.596	2,750,000	439,000	−0.094
6	98.6	76	16	0.792	+77.4	2,316	0.328	0.310	7.862	0.561	10.228		−1.117	2,950,000	363,000	−0.773
7	98.6	80	18	0.733	+64.4	2,005	0.324	0.272	11.188	0.622	15.162		−8.465	2,780,000	344,000	−1.922
8	98.6	76	16	0.822	+48.9	1,803	0.301	0.222	10.355	0.645	14.327		−8.560	.....	373,500	−1.587
9	98.6	72	16	0.756	+32.9	2,320	0.321	0.180	11.849	0.768	15.628		−7.956	.....	246,500	−1.272
10	98.6	72	16	0.774	+32.5	2,476	0.296	0.156	9.167	0.706	12.685		−4.765	.....	236,000	−0.535
11	98.6	70	16	0.803	+31.8	2,315	0.293	0.175	9.363	0.685	11.543	3.633	−3.756	.....	187,000	−0.498
12	98.2	68	14	0.767	+30.0	2,434	0.284	0.199	7.253	0.659	10.276		−2.349	.....	183,000	−0.288
13	98.0	70	16	0.838	+26.5	2,478	0.273	0.123	6.236	0.619	8.330		−0.303	.....	157,000	−0.052
14	98.0	68	14	0.829	+27.7	2,478	0.282	0.167	5.367	0.475	7.316		+0.710	.....	128,000	+0.112
15	98.0	68	14	0.844	+21.7	2,478	0.264	0.178	4.230	0.589	6.480		+1.547	.....	125,000	+0.139
16	99.0	68	16	0.776	+25.8	2,478	0.325	0.201	4.588	0.532	5.750		+2.276	.....	130,500	+0.053

* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. The changes following irradiation were the same as in case 1. If, as we contend, the period of increased oxygen consumption coincides with the height of induced protein catabolism, it would then appear that excretion of end-products may be considerably delayed. The nonprotein nitrogen of the blood was not followed.

TABLE 3.—*Data in Case 3*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	99.0	68	12	0.767	+40.5	3,503	0.479	0.193	6.928	0.361	8.317	7.623	+ 5.484	.....	320,800	+0.965
2	99.2	72	16	0.771	+40.9	3,308	0.650	0.145	7.807	0.546	10.282		+ 4.632	2,510,000	336,000	+0.386
3	99.2	68	16	0.739	+49.2	3,503	0.550	0.127	6.901	0.403	9.344		+ 4.458	.....	340,000	+0.905
4	99.2	72	16	0.715	+44.0	3,308	0.569	0.207	7.486	0.562	10.694		+ 4.219	.....	351,200	+0.409
5	99.4	70	16	0.735	+43.3	3,503	0.490	0.195	7.144	0.467	9.077		+ 4.724	.....	378,000	+0.918
6	99.2	72	16	0.739	+42.3	3,308	0.654	0.167	8.158	0.543	11.049		+ 3.864	.....	404,000	+0.407
7*	99.6	72	12	0.738	+40.5	2,465	0.591	0.244	8.226	0.591	10.505	5.008	— 1.454	2,820,000	392,000	—0.091
8	99.8	76	16	0.709	+52.2	945	0.550	0.231	8.407	0.656	11.097		—10.708	.....	371,000	—2.021
9	99.6	76	16	0.717	+44.6	1,154	0.605	0.245	10.383	0.731	16.704		—13.697	3,170,000	303,200	—1.639
10	99.0	72	14	0.730	+38.9	2,106	0.690	0.250	12.887	0.756	16.717		— 6.457	.....	284,000	—0.901
11	99.2	68	14	0.737	+41.5	2,065	0.497	0.246	9.832	0.735	13.416		— 4.328	.....	252,000	—0.529
12	99.2	68	12	0.766	+27.7	2,773	0.574	0.273	11.659	0.941	15.960		— 4.470	.....	132,000	—0.762
13	99.0	64	12	0.771	+28.3	2,700	0.550	0.192	9.442	0.764	12.810	7.650	— 1.805	.....	125,000	—0.693
14	98.6	64	12	0.770	+21.8	3,221	0.599	0.199	9.215	0.830	11.904		+ 2.752	.....	98,200	—0.253
15	99.2	64	12	0.732	+31.5	3,366	0.656	0.209	8.353	0.871	11.062		+ 2.742	.....	72,000	+0.109
16	98.6	68	14	0.713	+11.9	3,540	0.562	0.187	8.421	0.696	12.076		+ 2.833	2,800,000	72,000	+0.255
17	98.6	64	16	0.833	+19.6	3,352	0.705	0.160	7.303	0.851	9.917		+ 4.742	.....	72,000	+0.126
18	98.0	64	12	0.859	+11.6	3,532	.....	.....	.....	.....	.....		.....	.....	70,000	.....

* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. Irradiation was followed by a marked decrease in food intake so that a moderate increase in urinary nitrogen led to a marked loss of nitrogen from the body. The excretion of the excess nitrogen was more prompt than in cases 1 and 2. The induced protein catabolism may have been largely accomplished within the twenty-two hour period which elapsed between irradiation and the subsequent determination of the oxygen consumption.

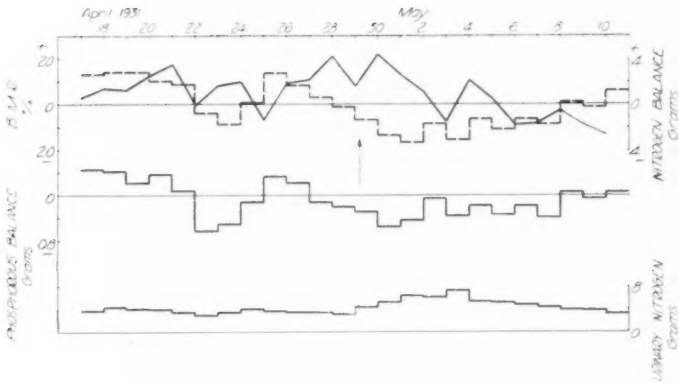


Chart 4.—Curves obtained during metabolic study in case 4. The arrow indicated irradiation.

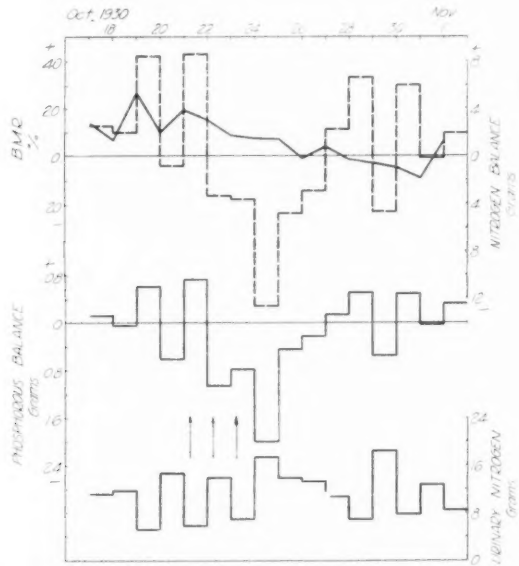


Chart 5.—Curves obtained during metabolic study in case 5. The arrows indicate irradiation.

TABLE 4.—*Data in Case 4*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	98.6	88	16	0.762	+ 2.5	1,756	0.236	0.211	2.633	0.261	3.726		+2.615	3,620,000	355,000	+0.460
2	99.2	84	16	0.740	+ 7.2	1,730	0.266	0.203	2.802	0.254	4.267		+2.900	3,120,000	346,000	+0.433
3	99.0	88	14	0.711	+ 6.5	1,713	0.225	0.188	2.935	0.322	4.141		+2.916	3,760,000	333,000	+0.233
4	99.0	84	16	0.696	+12.1	1,788	0.242	0.127	2.819	0.349	3.963	4.184	+2.047	3,800,000	314,000	+0.370
5	99.4	84	16	0.705	+17.7	1,418	0.215	0.125	2.411	0.385	3.470		+1.766	3,440,000	309,500	+0.086
6	99.2	80	16	0.712	— 0.5	470	0.211	0.111	1.925	0.384	3.003		−8.342	3,800,000	322,500	−0.627
7	99.4	84	16	0.704	+ 8.7	704	0.203	0.103	2.379	0.297	3.528		−1.899	3,530,000	366,000	−0.506
8	99.2	84	16	0.719	+10.4	976	0.213	0.149	3.085	0.292	4.069		+0.111	3,380,000	380,000	−0.122
9	98.6	80	16	0.704	— 6.5	1,364	0.238	0.219	2.641	0.285	3.748		+2.805	3,530,000	380,000	+0.341
10	99.4	84	16	0.728	+ 9.5	1,153	0.210	0.119	2.487	0.383	3.624	4.664	+1.574	3,210,000	346,000	+0.238
11	99.6	84	16	0.711	+11.0	987	0.246	0.188	2.681	0.403	3.559		+0.637	3,500,000	338,000	−0.117
12	99.2	84	16	0.700	+21.7	852	0.230	0.218	2.377	0.312	3.203		−0.189	3,800,000	326,000	−0.189
13*	99.6	84	16	0.755	+ 8.0	583	0.241	0.153	2.984	0.322	4.357		−1.262	3,690,000	371,000	−0.273
14	99.2	84	18	0.711	+22.1	628	0.279	0.201	3.888	0.501	5.252		−2.696	3,780,000	373,000	−0.564
15	99.6	84	16	0.700	+13.1	734	0.274	0.224	4.721	0.442	6.336		−3.346	3,270,000	218,000	−0.434
16	99.4	88	16	0.725	+ 6.0	912	0.281	0.216	4.951	0.541	6.112	1.695	−1.642	3,900,000	288,400	−0.062
17	99.4	84	16	0.706	— 7.5	868	0.264	0.187	5.678	0.605	7.253		−3.140	3,800,000	276,000	−0.371
18	99.0	80	16	0.699	+10.4	913	0.226	0.146	4.170	0.533	5.586		−1.242	3,300,000	170,000	−0.183
19	98.8	80	16	0.716	+ 3.0	752	0.223	0.101	3.952	0.439	5.105		−2.255	3,640,000	186,500	−0.339
20	98.8	76	14	0.728	— 8.8	830	0.221	0.146	3.493	0.508	4.794		−1.137	4,240,000	181,500	−0.170
21	98.8	72	14	0.706	— 6.1	679	0.227	0.144	2.989	0.511	4.270		−1.611	3,410,000	182,500	−0.386
22	98.8	72	16	0.716	— 2.2	1,025	0.218	0.134	2.951	0.733	3.998	1.999	+2.540	3,670,000	139,500	+0.077
23	98.6	72	16	0.766	— 8.1	909	0.226	0.133	3.031	0.345	3.932		−0.213	3,760,000	127,000	−0.066
24	99.6	80	16	0.701	—12.8	955	0.187	0.117	2.611	0.286	3.307		+1.244	3,720,000	122,000	+0.062

* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. The increase in oxygen consumption following irradiation was not great, a circumstance which is in keeping with the small increase in urinary nitrogen and the low caloric intake. The reaction of this patient may have been influenced by a roentgen treatment which was given eleven days before the metabolic observations were begun.

TABLE 5.—*Data in Case 5*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	98.6	68	10	0.827	+14.5	2,763	0.485	0.117	8.885	0.691	11.278	5.208	+2.637	3,910,000	82,500	+0.137
2	98.6	68	12	0.827	+ 6.9	2,878	0.597	0.173	8.751	0.662	11.923		+2.016	.....	65,000	—0.035
3	98.4	68	12	0.787	+27.0	2,878	0.310	0.101	3.800	0.337	5.401		+8.538	.....	67,500	+0.605
4	98.4	68	12	0.794	+ 9.6	2,878	0.790	0.211	10.555	0.631	14.756		—0.816	.....	56,500	—0.602
5*	98.2	72	12	0.809	+19.4	2,878	0.329	0.086	4.971	0.294	6.207	3.136	+8.512	.....	.....	+0.710
6*	97.8	72	12	0.785	+14.7	2,157	0.730	0.163	10.497	0.654	13.941		—3.295	.....	31,500	—1.077
7*	97.8	68	12	0.767	+ 7.9	1,185	0.321	0.096	5.962	0.436	7.484		—3.648	.....	24,800	—0.783
8	98.2	64	12	0.705	+ 7.3	860	0.715	0.350	12.658	0.940	17.482		—12.648	.....	.....	—2.002
9	98.0	60	12	0.750	+ 6.5	1,866	0.352	0.191	10.807	0.717	13.916		—4.778	.....	.....	—0.455
10	98.0	60	12	0.729	— 1.6	2,238	0.371	0.230	9.981	0.958	13.599		—2.989	.....	.....	—0.232
11	98.0	60	10	0.743	+ 3.5	2,386	0.472	0.134	8.082	0.930	10.563	6.902	+2.253	.....	.....	+0.151
12	98.0	60	10	0.732	— 1.2	2,688	0.321	0.065	4.929	0.590	6.785		+6.735	.....	.....	+0.502
13	98.0	60	10	0.812	— 3.0	2,725	0.910	0.260	14.196	1.764	18.396		—4.658	.....	.....	—0.567
14	97.2	60	10	0.801	— 5.0	2,776	0.508	0.090	6.055	0.704	7.806		+5.999	.....	.....	+0.485
15	97.0	60	10	0.735	— 9.6	2,601	0.677	0.164	9.722	1.098	12.858		—0.222	.....	.....	—0.029
16	98.0	60	10	0.782	+ 6.2	2,169	0.594	0.126	6.601	0.612	8.469		+1.976	.....	.....	+0.326

* Roentgen therapy (total 1,000 roentgens in three days). The complete absence of increase in oxygen consumption in this patient led us to undertake experiments of the type seen in chart 8.

CASE 2.—N. J., a white man, aged 55, had a condition diagnosed leukemic myelosis eighteen months before metabolic studies were begun, and during this interval fifteen or twenty roentgen treatments were given. The metabolic studies extended from Oct. 2 to 24, 1930. On October 13, the patient received a single roentgen treatment (500 roentgens) equally divided between the ventral and dorsal

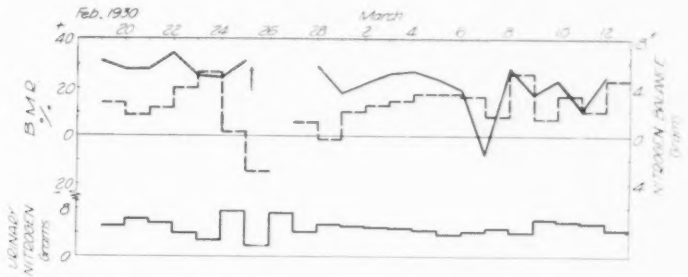


Chart 6.—Curves obtained during the first metabolic study in case 6. The arrow indicates an operation followed by hemorrhage and transfusion.

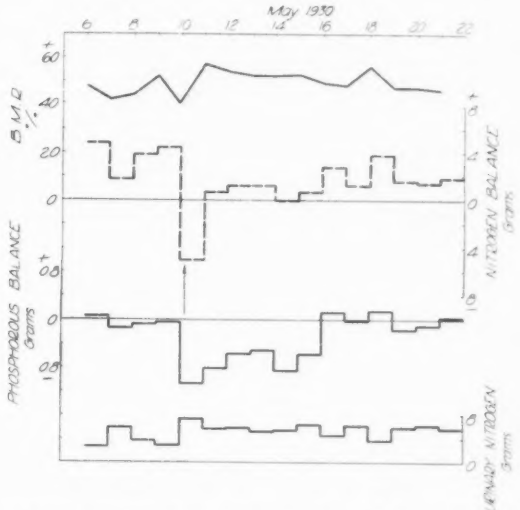


Chart 7.—Curves obtained during the second metabolic study in case 6. The arrow indicated irradiation.

aspects of the splenic region. Seven days later the long diameter of the spleen had decreased about 9 cm.

CASE 3.—E. F., a white man, aged 40, had an enlarged spleen in June, 1930, but received no irradiation prior to the period of metabolic study, which extended from Jan. 14 to 20, 1931. A single roentgen treatment (500 roentgens) was administered on January 20, and was equally divided between the ventral and

TABLE 6.—*Data in Case 6 Obtained During First Metabolic Study*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Calorie Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.
1	97.6	68	16	0.717	+30.7	2,562	0.345	0.175	3.473	0.169	5.267	3.731	+2.872	.....	.....
2	97.6	72	16	0.707	+28.4	2,562	0.447	0.212	4.328	0.235	6.374		+1.765	.....	.....
3	98.0	76	16	0.725	+28.0	2,562	0.395	0.119	4.231	0.293	5.656		+2.484	.....	.....
4	97.0	72	16	0.694	+34.6	2,562	0.267	0.066	2.846	0.193	3.968		+4.172	.....	.....
5	98.6	72	16	0.738	+25.3	2,562	0.190	0.048	1.873	0.141	2.764		+5.376	.....	.....
6	98.4	72	16	0.719	+24.9	2,562	0.522	0.226	5.675	0.352	7.749		+0.391	3,320,000	110,000
7*	98.2	80	16	0.728	+31.4	.....	0.150	0.036	1.357	0.094	1.928	9.422	−2.871	.....	.....
8	....	..	..	.....	.....	1,214	0.451	0.117	5.245	0.414	7.194		−3.347	.....	.....
9	....	..	..	.....	.....	1,282	0.260	0.046	2.716	0.224	4.147		+1.200	.....	.....
10	98.0	88	16	0.705	+28.7	1,930	0.323	0.052	3.027	0.349	5.298		−0.233	.....	.....
11	97.4	84	16	0.705	+17.4	2,595	0.375	0.048	3.206	0.382	5.284		+2.070	.....	.....
12	98.0	78	16	0.749	+22.1	2,563	0.312	0.057	3.289	0.369	4.950		+2.589	.....	.....
13	98.4	80	16	0.715	+26.3	2,656	0.293	0.050	3.322	0.343	4.882		+2.937	3,100,000	100,500
14	97.6	78	16	0.702	+27.1	3,033	0.320	0.079	3.287	0.280	4.351		+3.571	.....	.....
15	97.0	76	16	0.740	+23.6	2,786	0.255	0.071	2.797	0.221	3.790		+3.511	.....	.....
16	97.4	72	16	0.710	+18.8	2,402	0.209	0.039	2.907	0.249	4.155		+3.408	.....	.....
17	97.2	72	16	0.797	− 9.1	2,540	0.265	0.083	3.022	0.196	4.593	8.281	+1.766	.....	.....
18	97.4	76	16	0.702	+27.1	3,120	0.255	0.068	2.969	0.251	3.906		+5.258	.....	.....
19	97.4	76	16	0.721	+16.1	2,673	0.424	0.101	4.147	0.295	6.086		+1.411	.....	.....
20	98.0	72	18	0.724	+10.0	2,741	0.388	0.130	4.276	0.354	5.812		+3.352	.....	.....
21	98.0	72	16	0.781	+23.2	2,991	0.331	0.080	3.975	0.404	5.449		+2.048	.....	.....
22	97.8	74	16	0.715	+22.1	3,089	0.395	0.121	3.602	0.220	4.470		+4.714	.....	.....

* Operation, hemorrhage and transfusion. An attempt was made to compare the effects of surgical removal as contrasted with removal of tissue by irradiation. The hemorrhage and the transfusion interrupted the experiment at a crucial time.

TABLE 7.—*Data in Case 6 Obtained During Second Metabolic Study*

Days	Temperature, Mouth, F.	Pulse Rate, per Min.	Respiratory Rate, per Min.	Respiratory Quotient	Basal Metabolic Rate, per Cent	Caloric Intake	Creatinine, Gm. of Nitrogen	Uric Acid, Gm. of Nitrogen	Urea, Gm. of Nitrogen	Ammonia, Gm. of Nitrogen	Total Urinary Nitrogen, Gm.	Nitrogen in Stools, Gm.	Nitrogen Balance, Gm.	Erythrocytes, per C.Mm.	Leukocytes, per C.Mm.	Phosphorus Balance, Gm.
1	97.0	80	16	0.724	+48.1	2,137	0.166	0.088	2.155	0.160	2.833	3.220	+4.898	.....	.....	+0.061
2	97.8	80	18	0.730	+42.3	2,137	0.314	0.163	4.244	0.357	5.956		+1.775	.....	.....	—0.138
3	97.6	80	16	0.718	+44.6	2,137	0.219	0.118	2.732	0.219	3.760		+3.971	.....	.....	—0.075
4	97.4	80	18	0.732	+52.6	1,993	0.166	0.062	2.073	0.138	2.689		+4.407	.....	101,900	—0.038
5*	97.0	80	16	0.745	+40.9	1,129	0.355	0.176	5.008	0.413	7.453	8.477	—5.097	.....	.....	—1.076
6	97.8	80	16	0.727	+57.4	2,063	0.268	0.135	4.090	0.372	5.819		+0.776	.....	.....	—0.827
7	98.0	80	16	0.725	+53.8	2,137	0.275	0.138	4.022	0.367	5.891		+1.233	.....	.....	—0.576
8	97.0	80	16	0.757	+52.2	2,063	0.253	0.143	3.646	0.288	5.390		+1.205	2,550,000	118,000	—0.529
9	97.6	80	16	0.776	+52.2	1,919	0.261	0.173	3.949	0.335	5.545		—0.006	.....	.....	—0.868
10	97.0	80	16	0.720	+52.8	2,137	0.301	0.145	4.628	0.319	6.357		+0.765	.....	.....	—0.577
11	97.8	80	16	0.728	+49.4	2,137	0.213	0.100	3.451	0.219	4.648	6.139	+2.864	.....	.....	+0.123
12	97.4	80	16	0.757	+48.1	2,137	0.280	0.134	4.881	0.354	6.222		+1.291	.....	.....	—0.034
13	98.0	76	16	0.697	+56.3	2,137	0.184	0.087	2.714	0.212	3.677		+3.836	.....	.....	+0.140
14	98.0	80	16	0.743	+47.2	2,137	0.285	0.121	4.200	0.373	5.840		+1.673	.....	.....	—0.156
15	98.4	80	16	0.733	+47.4	2,137	0.297	0.110	4.264	0.366	6.072		+1.441	.....	.....	—0.101
16	98.2	80	16	0.754	+45.6	2,137	0.295	0.111	4.206	0.316	5.664		+1.848	.....	102,000	+0.045

* Roentgen therapy (300 roentgens) following determination of the basal metabolic rate. The dose of roentgen rays was smaller and the responses in both nitrogen and oxygen consumption were smaller than in cases 1 and 2.

dorsal aspects of the splenic area. The long diameter of the spleen decreased 10 cm. in the following seven days. The case was a characteristic example of leukemic myelosis.

CASE 4.—I. B., white woman, aged 49, had a condition diagnosed leukemic myelosis in July, 1930, and on April 6, 1931, received one roentgen treatment (200 roentgens). The period of metabolic study extended from April 17, to May 10, 1931. A single roentgen treatment (500 roentgens) was given on April 29, and was followed by a decrease of about 3 cm. in the long diameter of the spleen.

CASE 5.—In H. B., a white man, aged 37, symptoms were first noted in January, 1930. The diagnosis of leukemic myelosis was established, and three roentgen treatments were given in March, and three more in July, 1930. Metabolic studies were begun on October 17, and roentgen treatments were given on October 21, 22 and 23. The three irradiations during the period amounted to 1,000 roentgens, and were limited to the splenic area. Seven days after the last treatment, the spleen had decreased about 6 cm. in its long diameter.

CASE 6.—G. P., white man, aged 69, had enlarged lymph nodes that were discovered by the patient two and one-half years before our studies were begun. All of the characteristic features of lymphatic leukemia were present. Metabolic studies extended from February 19, to March 12, 1930. On February 25 a mass of lymphoid tissue 12 by 10 by 4 cm. and weighing about 500 Gm. was removed from the upper part of the sternum. Considerable blood was lost, necessitating a transfusion. A second metabolic study extended from May 6 to May 21, 1930. A dose of roentgen rays (300 roentgens) was given over the dorsal and ventral splenic areas on May 10. The long diameter of the spleen decreased only about 3 cm. after this treatment.

COMMENT

A study of the charts will reveal that there are two phases in the response of leukemic patients to roentgen rays. Immediately after irradiation there is a decided negativity in the nitrogen and phosphorus balances. This state of affairs is contributed to by decreased food intake and increased protein catabolism. Occasionally the former factor is by far the larger, and this is especially true in case 5. Another variable factor in this connection is the speed with which protein is catabolized after irradiation. This may depend in part on the amount of irradiation applied and the susceptibility of the cells and in part on the efficiency of the catabolizing and excretory mechanisms of the patient. At least in case 5 in which the symptoms were of recent origin, the excess uric acid excretion was accomplished more rapidly than in cases of longer standing, such as cases 1 and 2. This observation suggested the possibility that the increased oxygen consumption of protein catabolism after roentgen therapy might follow a curve more or less like that seen after the ingestion of protein. In consequence, the oxygen consumption was determined at hourly intervals after smaller doses of roentgen rays, and the resultant curves are shown in chart 8. Taking into account the numerous variable factors, we interpret these data as showing that irradiation in leukemia leads to an increased oxygen consumption during the time that protein is actually being catabolized.

This is exactly what might be expected since Rubner [32] has shown that endogenous protein has the same specific dynamic effect as exogenous protein, and Kikkoji [33] was able to show an increase in basal metabolic rate after the ingestion of radium water. The duration and extent of the increased oxygen consumption after irradiation no doubt depends on the degree of protein catabolism induced and the speed with which the catabolic products are completely metabolized. Musser and Edsall [34] described the effect of irradiation on the metabolism of nitrogen and phosphorus in leukemia. Riddle and Sturgis [7] and Krantz and Riddle [8]

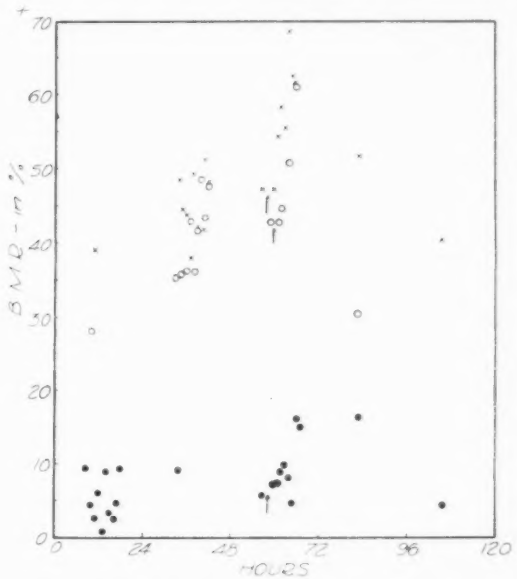


Chart 8.—Curves obtained during metabolic studies. The arrows indicate the points at which roentgen ray treatments were given. The doses varied from 150 to 300 roentgens and were given over the splenic areas. During both control and treatment days food was withheld, and the basal metabolic rate was determined every hour. It will be noted that the patients with higher initial metabolic rates responded more promptly and to a greater degree than the one in whom the oxygen consumption was within normal limits before irradiation. The cross indicates the curve of N. J. (April 15, 1931); the open circle, the curve for H. B. (May 17, 1931), and the solid circle, the curve for I. B. (Dec. 8, 1931).

32. Rubner, M., quoted by Lusk, G.: The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1928, p. 282.

33. Kikkoji, T.: Ueber den Einfluss von Radiumemanation auf den Gesamtstoffwechsel im Organismus, Radium, Biol. Heilkunst. **1**:46, 1911.

34. Musser, J. H., and Edsall, D. L.: A Study of Metabolism in Leukemia Under the Influence of the X-Ray, Univ. Pennsylvania M. Bull. **18**:174, 1905-1906.

found an occasional increase in basal metabolism in leukemic patients after irradiation, but we know of no previous systematic correlation of the two factors.

The second phase of the postirradiation reaction in leukemia is the direct opposite of the first. There is a tendency toward retention of nitrogen and phosphorus and a lowering of the oxygen consumption. This is in accordance with the findings which obtain during remissions in pernicious anemia. Protein catabolism usually reached a lower level during this period than in the control period.

Without data of a more quantitative nature, it seems futile to try to establish whether or not the increase in oxygen consumption can be completely accounted for on the basis of protein catabolism. For such calculations it would be necessary to keep the patient in a respiratory calorimeter almost constantly until the catabolism of the protein is completed. Neither the oxygen consumption nor the endogenous nitrogen excretion remain constant for long at a time, and major fluctuations throughout the day may be missed by our method of study.

It is our purpose in these communications to point out that the formation of blood elements is associated with a lowered total oxygen consumption, while the destruction of these same elements causes an increased basal metabolic rate. However, the application of these two principles in an explanation of the increased metabolism of untreated leukemia is beset with difficulties. Brogsitter and Schmidt-Ott [35] showed that patients with lymphatic leukemia who were on a minimum nitrogen intake excreted 2.6 to 3.2 mg. of uric acid per kilogram per day instead of the normal from 1.6 to 2.8 mg. per kilogram per day. The uric acid excretion of a patient with leukemic myelosis was found to be 4.8 mg. per kilogram per day under similar circumstances. These investigators estimated that leukocytes were being formed and destroyed at from thirty-six to fifty-six times the normal rate and were consequently forced to conclude that part of the nitrogen-containing material in the leukocytes was used over and over again. However, it would appear a priori that such nitrogen-containing elements which were to be reutilized would probably not be broken down past the amino-acid stage. We have no accurate information as to the amount of energy involved in the dissociation and detoxification of leukocyte proteins when this is done elsewhere than in the gastro-enteric tract. The normal destruction of leukocytes is accomplished largely at least by excretion into the gastro-enteric tract where they are digested and reabsorbed. The number of leukocytes in the saliva is increased after roentgen treatment

35. Brogsitter, A. M., and Schmidt-Ott, A.: Ueber den Eiweissstoffwechsel bei Leukämien im Stickstoffminimumversuch, Deutsches Arch. f. klin. Med. **170**:1, 1931.

in leukemia, but it seems unlikely that all cells disappearing from the spleen after irradiation could find their way into the gastro-enteric tract. On teleologic grounds one might expect a disturbance in metabolism from the breaking up of leukocytes within the physiologic limits of the body instead of in the digestive tract. Experimental evidence on this point is difficult to obtain because the parenteral introduction of protein is so frequently complicated by "foreign protein reactions."

The experimental work of Mann [36] and his co-workers, of Dock,[37] of Meyerhof, Lohmann and Meier [38] and of Bornstein and Roese [39] all tends to show that deamidization of amino-acids by the liver is necessary before the specific dynamic effect of these substances becomes apparent. If these findings are correct, it probably would not be possible for the amino-acids which result from leukocyte destruction to exert a specific dynamic effect and to be reutilized subsequently. There seems to be no good reason for assuming that the resynthesis of amino-acids is of any greater magnitude in leukemia than in the normal. Boothby, Sandiford and Giffin [40] found an increased amino-acid content of the blood in leukemia. Rapport and Katz [41] found that the addition of an amino-acid to the defibrinated blood with which an isolated hindleg was perfused, increased the oxygen up-take of the tissue. These two observations would suggest that the increased oxygen consumption of leukemia might be due to a catalytic effect of circulating amino-acids. However, Bornstein [39] was unable to confirm the work of Rapport and Katz, which is also directly opposed to the findings of other investigators.[42]

That the metabolism of amino-acids derived from ingestion of protein is associated with an increased oxygen consumption is certainly not debatable. A similar rise is seen if the pure amino-acids are injected intravenously. Under ordinary circumstances, the specific dynamic action of food is intentionally missed by determining the basal metabolic

36. Mann, F. C.; Wilhelmj, C. M., and Bollman, J. L.: Studies on the Physiology of the Liver, Am. J. Physiol. **81**:496, 1927; **87**:497, 1928.

37. Dock, W.: The Relative Increase in Metabolism of the Liver and Other Tissues During Protein Metabolism in the Rat, Am. J. Physiol. **97**:117, 1931.

38. Meyerhof, O.; Lohmann, K., and Meier, R.: Ueber die Synthese des Kohlenhydrats im Muskel, Biochem. Ztschr. **157**:459, 1925.

39. Bornstein, A., and Roese, H. F.: Ueber die Beeinflussung des Sauerstoffverbrauches überlebender Organe durch Glykokoll, Arch. f. ges. Physiol. **223**:498, 1929.

40. Boothby, W. M.; Sandiford, I., and Giffin, H. Z.: The Amino-Acid Nitrogen in the Blood and Its Possible Relation to the Elevated Metabolism in Myelogenous Leukemia, J. Biol. Chem. **55**:xxiii, 1923.

41. Rapport, D., and Katz, L. N.: The Effect of Glycine upon the Metabolism of Isolated Perfused Muscle, Am. J. Physiol. **80**:185, 1927.

42. Mann and others.[36] Dock.[37]

rate during the postabsorptive period. In leukemia metabolism of amino-acids from broken down leukocytes is perhaps a variable but more or less constant factor which cannot be avoided in the determination of the basal metabolic rate. The protein turn over in leukocyte destruction is perhaps large enough to simulate the conditions which obtain in the "secondary rise" of Rubner or the "luxus consumption" of other writers. It is possible that immature cells have a greater rate of destruction than the more adult forms, and this may be an explanation for the relationship observed by previous investigators [43] between the number of circulating immature cells and the basal metabolic rate. There is much evidence that an undue increase in endogenous protein catabolism may cause a rate of oxygen consumption of a magnitude comparable to that seen in leukemia. This is perhaps best shown in phlorhizin diabetes.[44]

The increased oxygen consumption which follows irradiation of the spleen in leukemia is no doubt the result of increased protein catabolism. Such factors as cell growth, cell activity and increased numbers of leukocytes are, we believe, utterly inadequate as an explanation for the increased gaseous metabolism in leukemia. We believe, therefore, that the virtue of logic is with the contention that protein catabolism is in some way responsible for the major part of the increased oxygen utilization of the leukemic patient. The mechanism by which protein catabolism brings this change about is not clear. The effect of autolysis of leukocytes in tissue is one of the unknown and possibly important factors. Until the intermediary metabolism of protein in general is better understood, the details will remain obscure.

SUMMARY

An hematopoietic disease (leukemia) has been studied before and immediately after irradiation. Immediately after roentgen treatment there is increased protein catabolism which is derived largely from the destruction of nucleated cells. The evidence for this statement is to be found in the increased excretion of uric acid and perhaps of phosphorus. This accentuation of cellular destruction is associated with an increase in the total oxygen consumption of the patient in most, if not all, instances. In the instance (case 5) in which no increase was observed, it appears that the catabolic processes were prompt and may have been completed within twenty-four hours after the treatment. The secondary phase which follows is characterized by increased nitrogen retention and a lowered total oxygen consumption.

43. Riddle and Sturgis.[7] Krantz and Riddle.[8] Gunderson.[9]

44. Lusk, G.: Animal Calorimetry: An Investigation into the Causes of the Specific Dynamic Action of Foodstuffs, J. Biol. Chem. **20**:555, 1915.

Evidence is presented to show that such factors as increased numbers of leukocytes in the body, increased activity of the hematopoietic tissues and anemia are entirely inadequate as explanations of the increased oxygen consumption in leukemia. We wish to suggest that protein catabolism is in some way the major factor in the increased gaseous metabolism of leukemia. The details as to how this cause brings about the result which it does are not clear. The evidence presented here substantiates the following previously suggested hypothesis: There is a direct causal relationship between the increase in nitrogen catabolism and the increased oxygen consumption and a similar relationship of cause and effect between nitrogen storage and decrease in oxygen requirement.

TREATMENT OF POLYCYTHEMIA VERA (ERYTHREMIA) WITH SOLUTION OF POTASSIUM ARSENITE

CLAUDE E. FORKNER, M.D.

T. F. McNAIR SCOTT, M.R.C.P. (LONDON)
AND
S. C. WU, M.D.
BOSTON

Arsenic has been used extensively for hundreds of years in the treatment of many diseases. During the past one hundred and fifty years it has been employed most commonly in the form of solution of potassium arsenite, U. S. P. (Fowler's solution). One of its chief uses, prior to a few years ago, was to combat anemia. There appears to be no doubt that prior to the discovery by Minot and Murphy [1] of the effectiveness of liver in pernicious anemia, solution of potassium arsenite properly given was responsible for many remissions produced in this disease.[2] Hence, arsenic gained the reputation of being an antianemic drug and was employed, frequently with a measure of success, in the treatment of certain types of anemia. On the basis of these facts, it would seem to be paradoxical that any favorable effect could be elicited by its administration to patients suffering from polycythemia vera.

No actual demonstration of the value of potassium arsenite or other preparations of arsenic in polycythemia vera can be found in the literature, although Turk,[3] in 1904, suggested the use of arsenic, having found, in one case of polycythemia vera, that the administration of solution of potassium arsenite in doses of 30 minims (1.9 cc.) daily was associated with a decrease in the hemoglobin concentration from 22 to 18 Gm. per hundred cubic centimeters of blood and a decrease in the erythrocyte count from 9,200,000 to 7,800,000 cells per cubic millimeter.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard University Medical School.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

2. Bramwell, B.: Anemia and Some of the Diseases of the Blood-Forming Organs and Ductless Glands, Edinburgh, Oliver & Boyd, 1899. Minot, G. R., and Forkner, C. E.: Unpublished Observations.

3. Turk, W.: Beiträge zur Kenntnis des Symptomenbildes der Polycythämie mit Milztumor und Zyanose, Wien. klin. Wchnschr. **17**:153 and 189, 1904.

Forkner and Scott [4] have recently reevaluated the use of solution of potassium arsenite in leukemia and have shown that its administration to patients with chronic myelogenous leukemia regularly brings about remissions during the earlier course of the disease. The remissions are characterized by: reduction of the total leukocyte count to normal or near normal, marked reduction in number, or in some instances complete disappearance, of immature cells from the blood, lessening of the anemia with usually a return to normal of hemoglobin and erythrocyte values; reduction in size of the spleen and of the liver, reduction in the basal metabolic rate and marked subjective improvement. Such remissions can be maintained for several months when the drug is continued in small doses. This treatment for leukemia is purely palliative and comparable to the effects obtained by roentgen or radium irradiation.

There exist certain analogies in the treatment of polycythemia vera and of chronic myelogenous leukemia. Both of these diseases are favorably influenced by intensive treatment with radium or high voltage roentgen rays. The blood picture is at least temporarily improved in each of these diseases by the administration of benzene.

Because of the analogies between the two diseases, it became pertinent to test the effectiveness of the administration of arsenic to patients with polycythemia vera. The effects have been studied in six patients. In each case there has been improvement in the hematologic manifestations, and in five cases the red blood cell and hemoglobin values have returned to or close to normal. The improvement in the state of the blood has been associated with subsidence or disappearance of subjective symptoms. All of the patients have received solution of potassium arsenite by mouth in the amounts indicated on the charts. They have received no other treatment during the course of or immediately preceding the period of study.

REPORT OF CASES

CASE 1 (chart 1).—*History.*—A 56 year old Irish laborer, whose chief complaint was "skin trouble" of five years' duration, was perfectly well until the gradual onset of skin lesions on the body, chiefly on the legs and trunk. They were described as small, reddish, somewhat elevated itching lesions, varying in size and in the degree of itching produced. Because of the persistence and spreading of the lesions, the patient came to the hospital, where the condition was diagnosed as dermatitis medicamentosa. However, no cause could be found

4. (*a*) Forkner, C. E., and Scott, T. F. M.: Arsenic as a Therapeutic Agent in Chronic Myelogenous Leukemia: Preliminary Report, J. A. M. A. **97**:3 (July 4) 1931. (*b*) Forkner, C. E.: The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, M. Clin. North America **15**:1057, 1932.

in the habits or history of the patient. The skin lesions have persisted, although fluctuating in intensity, to the present time.

Three years before admission to the hospital the patient noticed that his face was becoming red, and he considers that the intensity of the color has gradually increased. Also he began to have severe headaches, chiefly vertical and frontal, occurring almost daily and lasting several hours. These headaches gradually decreased in frequency and during the past one and one-half years they have not recurred. It was noticed by the patient about three years ago that a coarse tremor of his arms and hands was developing which has persisted without much change for the last two years. This tremor in itself has not been sufficient to interfere with his activities. The patient has lost about 40 pounds (18.1 Kg.) in body weight during the last three years. He believes also that his strength has decreased gradually during this time. Occasional moderate epistaxis occurred during the past three years, but no other tendencies to bleed were noticed.

The family history was not significant and contained no reference to polycythemia, leukemia, anemia, cancer or any familial disease.

The past history was not remarkable.

Physical Examination.—The following significant findings were revealed on examination: (1) intense deep red color (erythrosis) of the face and skin in general; (2) papular, macular and pustular reddish, slightly scaly, irregular, excoriated skin lesions a few millimeters in diameter scattered over the body, chiefly on the face and extremities; (3) moderately cyanotic mucous membranes; (4) engorged and deep red blood vessels of the retina; (5) rumbling systolic murmur over the apex of the heart; (6) blood pressure, 135 systolic and 85 diastolic; (7) spleen, 4 cm. below the costal margin with rounded, smooth edge, and (8) liver, 2 cm. below the costal margin, smooth and not tender.

Laboratory Data.—The urine and stool were not abnormal. The Wassermann reaction of the blood was negative. There were 9,610,000 red blood cells per cubic millimeter and hemoglobin, 169 per cent (26.36 Gm. per hundred cubic centimeters of blood). The red blood cells were normal in size and shape. There was no polychromatophilia or stippling. The white blood cells were 13,000 per cubic millimeter.

The differential count of the white blood cells was as follows: polymorphonuclear neutrophils, 80 per cent; polymorphonuclear eosinophils, 4 per cent; neutrophilic metamyelocytes, 2 per cent; small lymphocytes, 6 per cent; intermediate sized lymphocytes, 2 per cent, and monocytes, 6 per cent. The blood platelets were moderately increased in number.

The patient had been observed by other physicians prior to being seen in our clinic, and his blood had remained essentially as recorded for several months before treatment was commenced. During the three weeks immediately preceding therapy we observed him critically and did not note any essential changes either in his clinical condition or in his blood.

Solution of potassium arsenite was administered by mouth in 100 cc. of orange juice three times daily immediately after or with meals. The medicine was begun in doses of 5 minims (0.3 cc.) three times daily for two days, then increased to 6 minims (0.36 cc.) three times daily for two days and subsequently increased in this fashion to 10 minims (0.6 cc.) three times daily. Thereafter the dose was increased more slowly, only 1 minim (0.06 cc.) per day being added until the patient received 17 minims (1.05 cc.) three times daily. The medicine then was decreased by 1 minim per day to 8 minims (0.5 cc.) three times daily, on which dose the patient remained for one week. Because the erythrocyte count and hemoglobin

value were not yet normal, the dose was again gradually increased to 18 minims (1.12 cc.) three times daily and thereafter decreased. Medication was then discontinued for two months and another course of treatment followed.

Chart 1 illustrates the effects on the blood cells and also shows the reduction of the basal metabolic rate brought about as the result of treatment. The red blood corpuscles were reduced from 9,610,000 to 4,790,000 per cubic millimeter and the hemoglobin from 169 per cent (26.36 Gm. per hundred cubic centimeters of blood) to 95 per cent (14.82 Gm. per hundred cubic centimeters of blood).

After the patient had been taking solution of potassium arsenite for three months and was receiving about 50 minims (3.08 cc.) daily, there was a rather rapid fall in the number of erythrocytes. This was associated with the appearance of jaundice and with an icteric index of 29 units and a bilirubin of 5.5 mg. per hundred cubic centimeters of serum in the blood. The jaundice gradually disap-

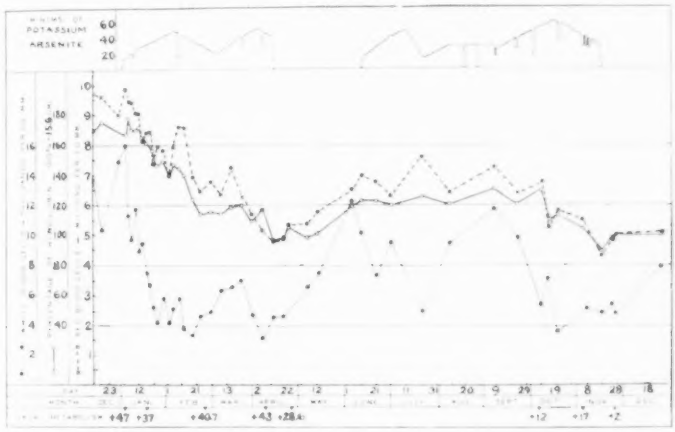


Chart 1.—Results of medication in case 1.

peared over a period of a few weeks, and presumably was due to increased blood destruction. There was no associated pain, tenderness or increase in size of the liver.

This improvement in the blood was associated with other signs of betterment manifested by moderate decrease in the size of the liver and the spleen, decrease in the intensity of the erythrosis of his skin and mucous membranes, almost complete disappearance of the skin lesions, gain in body weight and strength and subjective improvement.

The other five cases need not be discussed in detail. They represented typical cases of polycythemia vera. Charts 2, 3, 4 and 5 and the table illustrate the effects produced by essentially the same treatment as in the first case. However, there was considerable variation in the amount of solution of potassium arsenite needed to produce the desired result. No other patient required as large doses as did the first one.

Case 2 (chart 2).—A 67 year old man, who had been known to have had polycythemia vera for at least five years, complained of weakness, nervousness, sleeplessness and attacks of giddiness. Several months prior to coming under our observation he had been treated with phenylhydrazine hydrochloride, 0.1 Gm. daily or twice daily, until a total of 3.6 Gm. had been taken, which resulted in little improvement either in his blood or in his clinical condition. He had also received intensive treatment with high voltage roentgen rays applied only to the lower extremities. No improvement followed, probably owing to insufficient treatment.

When first seen in our clinic his blood contained 9,190,000 erythrocytes and 21,000 leukocytes per cubic millimeter. The hemoglobin was 133 per cent (20.75

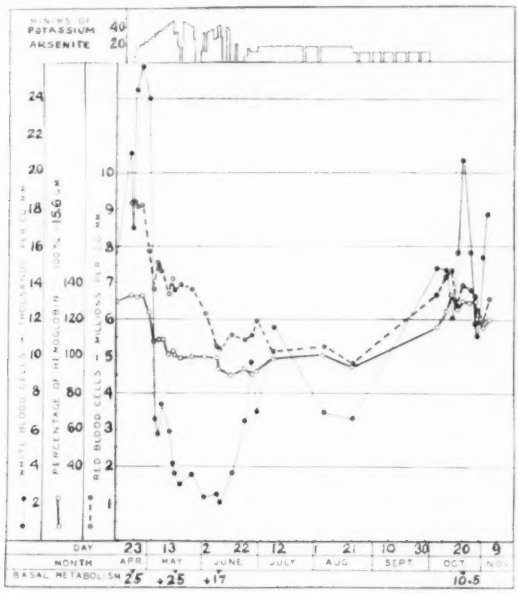


Chart 2.—Results of medication in case 2.

Gm. per hundred cubic centimeters of blood). The hematocrit reading was 69 per cent erythrocytes. As the result of treatment with solution of potassium arsenite the erythrocyte count fell to as low as 4,820,000 cells per cubic millimeter and the hemoglobin to 90 per cent (14.04 Gm. per hundred cubic centimeters of blood). The hematocrit reading was reduced to normal (43.2 per cent). The patient became subjectively well, and on small doses of solution of potassium arsenite, from 4 to 5 minims (0.24 to 0.3 cc.) three times daily, he remained free of symptoms for about five months. A relapse followed during which his erythrocytes increased to about 7,000,000 per cubic millimeter. The medication was increased (not shown on chart), and another remission was similarly induced.

Case 3 (chart 3).—A 62 year old Russian Jewish peddler, with polycythemia vera of six years' duration, complained of headache, restlessness, insomnia and

weakness. While receiving solution of potassium arsenite his erythrocyte count fell from 7,500,000 to 5,600,000 cells per cubic millimeter and the hemoglobin value from 125 per cent (19.5 Gm. per hundred cubic centimeters of blood) to 105 per cent (16.38 Gm. per hundred cubic centimeters of blood). Symptomatically, he was moderately improved. Several months after omission of the drug the erythrocyte and hemoglobin values again increased, with a return of symptoms.

CASE 4 (chart 4).—A 17 year old American schoolboy had polycythemia vera for at least four and one-half years. The chief symptoms were headaches, giddiness and pain in the left upper abdominal quadrant. His blood contained 8,250,000 erythrocytes and 20,000 leukocytes per cubic millimeter. The hemoglobin was 122 per cent (19.03 Gm. per hundred cubic centimeters of blood). The hematocrit reading was 63.6 per cent cells. The reduction of the erythrocyte and hemoglobin values in this patient were not as prompt or as dramatic as in the others, but when

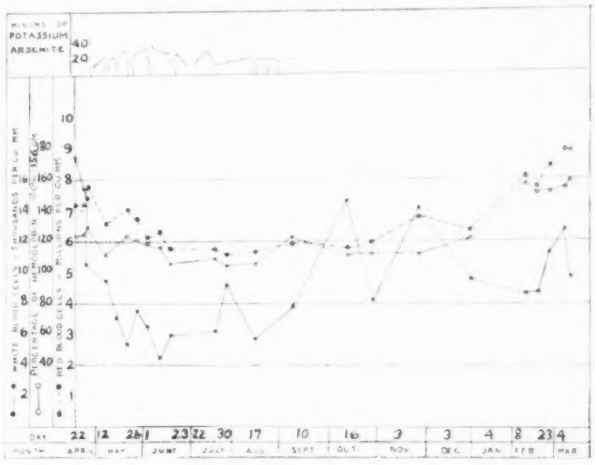
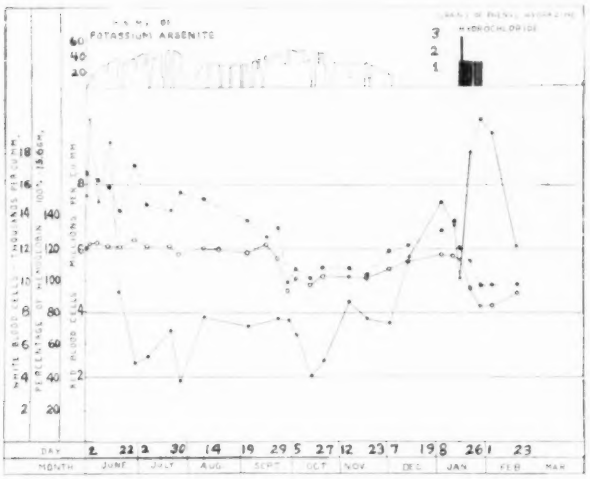


Chart 3.—Results of medication in case 3.

the medicine was pushed to the full limit of tolerance the red blood cells were reduced to as low as 4,720,000 per cubic millimeter and the hemoglobin to as low as 84 per cent (13.1 Gm. per hundred cubic centimeters of blood). The hematocrit reading was reduced to 47 per cent cells.

CASE 5.—The patient had had polycythemia vera for at least three years. He complained of sleeplessness, nervousness, acne and discoloration of the face. No treatment had been given for the polycythemia. Treatment with solution of potassium arsenite reduced the erythrocyte count from 8,540,000 to 6,665,000 per cubic millimeter, and the hemoglobin from 155 per cent (24.18 Gm. per hundred cubic centimeters of blood) to 130 per cent (20.28 Gm. per hundred cubic centimeters of blood) in seven weeks. The patient, however, seemed to be hypersensitive to the medicine, and it was discontinued before adequate treatment could be carried out.

CASE 6 (chart 5).—A 35 year old man had had polycythemia vera for about one year and complained of headache, nervousness and sleeplessness. Under treatment



Cart 4.—Results of medication in case 4. In this, as in the other charts, ●———● represents red blood cells, millions per cubic millimeter; ○———○ hemoglobin, percentage, and ●———● white blood cells, thousands per cubic millimeter.

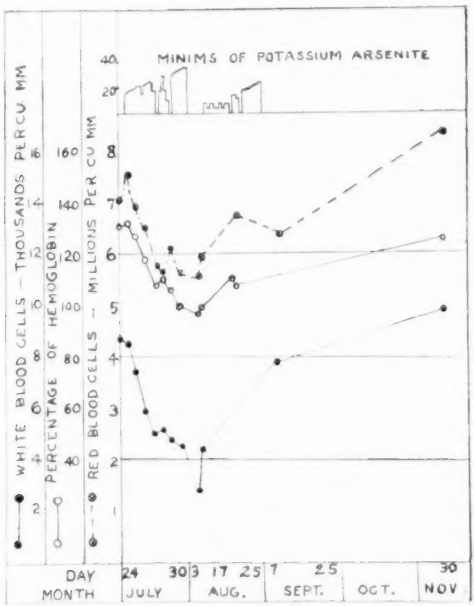

MINIMS OF POTASSIUM ARSENITE
WHITE BLOOD CELLS – THOUSANDS PER CU MM
PERCENTAGE OF HEMOGLOBIN
RED BLOOD CELLS – MILLIONS PER CU MM
DAY
MONTH
24 30 3 17 25 7 25 30
JULY AUG. SEPT. OCT. NOV

Chart 5.—Results of medication in case 6.

with solution of potassium arsenite the number of erythrocytes decreased from 7,250,000 to 5,620,000 per cubic millimeter, and the hemoglobin from 131 per cent (20.44 Gm. per hundred cubic centimeters of blood) to 98 per cent (15.23 Gm. per hundred cubic centimeters of blood). However, this patient was very uncooperative, rarely took the medicine with regularity and eventually was lost sight of altogether. It is seen from chart 5, however, that at the last examination, several months after discontinuing medication, another relapse had occurred.

The accompanying table permits us to make an analysis of the foregoing cases with reference to the time, after the commencement of treatment, when improvement occurred. At the end of ten days after the beginning of medication, in each case there was a decrease in the erythrocytes: the hemoglobin had fallen in four of the cases and usually the leukocytes were fewer.

After twenty days there was in three cases a further significant fall in the number of red blood cells and in the concentration of hemoglobin, and in one of these cases the number of erythrocytes and the hemoglobin value had returned practically to normal. The remaining three cases showed practically no further change until treatment had been continued for a longer time. This lack of uniformity may be explained by variations in the amount of solution of potassium arsenite administered and the precise state of the bone marrow and circulating blood.

After thirty days of treatment the blood remained about the same as after twenty days of treatment, except that as a rule there was greater leukopenia. These facts are illustrated on the charts 1, 2, 3 and 4, where also it may be observed that soon after the commencement of treatment there occurred a significant fall in the number of red blood cells and in the concentration of hemoglobin. Then in five of the six cases no further important decrease in the erythrocyte and hemoglobin values occurred over a period of from ten to thirty days. When the drug was pushed to near the limit of tolerance, the number of erythrocytes and hemoglobin percentage showed a further decrease.

From the table it may be seen that the number of erythrocytes and the percentage of hemoglobin returned practically to normal in one case after twenty days, in two cases after fifty days and in two others only after one hundred and twenty days of treatment. The sixth patient was unable to continue taking the medicine on account of being especially sensitive to it. In each instance the subjective and objective improvement began to appear after about ten days of treatment, when as a rule, the first significant fall in the number of red blood cells and hemoglobin percentage occurred.

Five of the six patients, prior to treatment, had an increased total number of leukocytes in the blood, and all had a greater than normal percentage of polymorphonuclear neutrophils. Mild to moderate

*Effect of Solution of Potassium Arsenite in Polycythemia Vera**

	Case 1			Case 2			Case 3			Case 4			Case 5			Case 6		
	Red Blood Cells	Hemoglobin	White Blood Cells	Red Blood Cells	Hemoglobin	White Blood Cells	Red Blood Cells	Hemoglobin	White Blood Cells	Red Blood Cells	Hemoglobin	White Blood Cells	Red Blood Cells	Hemoglobin	White Blood Cells	Red Blood Cells	Hemoglobin	White Blood Cells
Prior to treatment.....	9.61	169	13.00	9.19	133	21.00	7.50	125	15.45	8.25	122	20.00	8.54	155	18.00	7.25	131	8.50
After 10 days of treatment.....	9.10	170	11.80	7.81	124	24.00	6.63	112	9.45	7.88	121	18.50	7.90	147	16.85	5.75	109	5.00
After 20 days of treatment.....	7.37	156	5.15	6.68	101	5.95	6.84	118	7.05	7.11	120	9.20	8.01	143	8.60	5.62	100	4.50
After 30 days of treatment.....	7.01	140	4.20	6.94	99	3.10	6.71	121	7.50	7.37	121	5.20	7.73	153	3.60	5.96	98	4.35
After 50 days of treatment.....	6.46	114	4.65	5.24	93	2.10	5.81	106	5.90	7.16	121	6.85	6.67	130	5.80			
After 70 days of treatment.....	6.30	114	6.30	5.99	92	7.00	5.72	109	6.15	7.52	120	7.75	Medication discontinued					
After 90 days of treatment.....	5.69	109	4.65	5.14	99	11.60	5.70	106	5.60	6.89	117	7.15						
After 120 days of treatment.....	5.37	98	6.60	4.82	94	6.65	6.05	122	7.75	4.94	93	7.55						

* The erythrocytes are measured in millions per cubic millimeter; leukocytes in thousands per cubic millimeter, and hemoglobin in per cent (100 per cent = 15.6 Gm. per hundred cubic centimeters).

leukopenia occurred in each case as the result of treatment with solution of potassium arsenite. In no instance did the leukopenia decrease below 2,100 white blood cells per cubic millimeter. There occurred no significant change in relative numbers of the different kinds of white blood cells.

In addition to the six cases recorded, Dr. George R. Minot has informed us that he has treated two additional patients, according to the methods we have advised, with entirely satisfactory results.

UNTOWARD EFFECTS OF TREATMENT WITH ARSENIC

During the course of treatment of various types of patients with large amounts of solution of potassium arsenite there usually occur some signs or symptoms of toxicity. The character of these effects depends on several factors, chief of which seems to be the susceptibility of different persons to arsenic. Other factors are: the quantity of the arsenic ingested with each dose, the amount of dilution of the medicine and the relation of the time of meals to the time of taking the medicine.

Some patients with polycythemia and with leukemia respond to relatively small, and other patients to relatively large, doses of solution of potassium arsenite. We have discovered no explanation for this variability, but it is possible that it may depend on the amount of involvement of the bone marrow.

Loss of appetite and later mild nausea are perhaps the most common early symptoms, indicating that the limit of tolerance for solution of potassium arsenite is being approached, and that if the drug is to be given in larger doses the rate of increase must be gradual. Patients rarely need to vomit as the result of receiving too much of the drug. Vomiting usually indicates that the medicine has been increased too quickly, or that the patients' gastro-intestinal tract is in an unusually irritable state. Diarrhea consisting of from four to six rather loose movements daily is a common symptom when the larger doses of the drug are taken.

Chemosis of the conjunctivae, lasting a few days, occurred in two of our six patients with polycythemia vera and was a troublesome, but not a serious complication.

Slight burning sensations in the toes and fingers occur occasionally in patients under treatment with solution of potassium arsenite, but no permanent changes associated with these sensations have been observed.

Peripheral neuritis is said to follow administration of arsenic in rare instances. We have not observed this complication in the treatment in the cases reported in this paper or in the treatment of about thirty other patients with other diseases.

Herpes zoster along the course of the sixth left intercostal nerve occurred in the second case reported, but not during the period of observation shown on the chart. This patient had received solution of potassium arsenite almost continuously over a period of five and one-half months. It was then discontinued for three months and resumed, but owing to a misunderstanding the patient received the medicine much too rapidly. In the course of six days the dose had been increased from 15 to 35 minims (0.92 to 2.16 cc.) daily and then was decreased to 21 minims (1.31 cc.) daily. It was on the ninth day following the beginning of this second course of treatment that the herpes zoster occurred. In a total of thirty-five cases, representing various diseases, particularly leukemia, we have noted, during treatment with solution of potassium arsenite, herpes zoster to develop in five, an incidence of 14.3 per cent. This is possibly a somewhat higher incidence than is to be expected in similar cases under other forms of treatment. Owing to misunderstood orders, four of the five patients in whom herpes zoster developed received the drug in a grossly irregular manner or in too rapidly increasing amounts. The herpes zoster took the usual course, and in no instance has it left any permanent damage.

Pigmentation of the skin and hyperkeratosis have been reported following in the wake of long-continued treatment with solution of potassium arsenite. In two of the cases reported in this paper, in one instance after five and one-half months, and in the other after ten months of almost continuous medication, some slight thickening and drying of the skin of the palms of the hands and soles of the feet developed which persisted for a few weeks and then entirely disappeared after the arsenic temporarily had been omitted.

In one of the patients with polycythemia vera mild transient jaundice developed at the time when the red blood cells were decreasing rapidly, presumably due to destruction of the cells. It is possible that this jaundice could have been due to liver damage, but this seems unlikely in view of the fact that jaundice has not occurred in any of the patients with chronic leukemia whom we have treated, some of whom have received large doses of solution of potassium arsenite continuously for as long as nine months.

METHOD OF ADMINISTERING SOLUTION OF POTASSIUM ARSENITE

From our experience we feel that the best results can be obtained by adhering to the rules given here. In a previous publication [4b] it was suggested that the first dose should be about 5 minims of solution of potassium arsenite three times daily. We are now of the opinion that beginning doses of 3 or 4 minims (0.18 or 0.24 cc.) three times daily are somewhat better borne at the start and produce as satisfactory

results. This initial dose is continued for two days, and then the total daily dose is increased by 3 minims. This amount is given for two days. Thereafter the dose is increased at the same rate until the first sign of intoxication, anorexia, is noted. This sign, as a rule, is first noticed when the dose reaches about 24 minims (1.48 cc.) daily. When this dose of 8 or 10 minims three times daily has been reached, or earlier if indicated, the subsequent increments in amounts of the drug must be added more slowly at the rate of an increase of not more than 1 minim to the total daily dose. By such a method medication may be carried up to 12, 15 or even 20 minims (0.74, 0.92 or 1.25 cc.) three times daily.

The policy we have found of most value is to continue increasing the medicine until desired effects are obtained or until the limit of tolerance has been reached. Frequently, the best therapeutic results are to be obtained with the dose which is near the upper limit of tolerance. With solution of potassium arsenite, as with many other drugs, the tendency is to give too little rather than too much. Mild toxic symptoms are to be disregarded, or the best results often will not be obtained.

When the blood has improved considerably or when the limit of tolerance has been reached, the solution of potassium arsenite gradually should be withdrawn. The total daily dose may be decreased by 1 minim daily until the patient is taking about 5 minims three times daily, which amount may be continued without harm for at least several months. If, with the larger doses, rather severe toxic symptoms develop, the drug may be entirely omitted for forty-eight or seventy-two hours and then resumed in doses equivalent to about three fourths or two thirds of the amount which the patient was taking at the time of the development of the symptoms. From this point the drug may again be increased or may be decreased as indicated by the effects on the patient.

The medicine is best given either with or immediately after meals well diluted in orange or tomato juice or some other flavored drink.

COMPARISON OF THE USE OF SOLUTION OF POTASSIUM ARSENITE WITH OTHER METHODS OF TREATING POLYCYTHEMIA VERA

There exist essentially three methods of treatment of polycythemia vera: (1) venesection at intervals, (2) administration of phenylhydrazine, usually as hydrochloride and (3) irradiation by means of radium or high-voltage roentgen rays. No other methods have been shown to be of any distinct value. None of the foregoing methods are curative. The first is of very transient value and is wrong in principle in that the removal of blood acts as a stimulus for new blood formation.

The administration of phenylhydrazine is frequently effective in reducing the polycythemic aspects of the disease, but it is a drug which must be given with extreme care because of its cumulative and frequently delayed action. Thromboses of blood vessels occur frequently following treatment with phenylhydrazine, more frequently than with any other treatment.[5] Phenylhydrazine improves the blood of the polycythemic patient by destruction of red blood cells and does not in any way produce a more normal formation of blood. The third method of treatment, that of irradiation, has as its purpose the inhibition of the abnormal function of the bone marrow.

Although, in the absence of any knowledge as to the etiologic agent, it is impossible to discuss with certainty the rationale of any form of therapy, this later method of irradiation appears to be more logical and of more prolonged value than the other two methods, providing an adequate amount of treatment is skilfully given.

Arsenic in the form of solution of potassium arsenite appears to act chiefly to depress the activity of the bone marrow,[6] but at the same time in large doses it perhaps may hasten the destruction of erythrocytes.

From the study of these six cases of polycythemia vera and of two additional cases observed by Dr. George R. Minot, it is suggested that the administration of solution of potassium arsenite is a safe and reliable method, which may be used alone or in conjunction with other methods for the palliative treatment of polycythemia vera.

SUMMARY AND CONCLUSIONS

1. Six patients with polycythemia vera have been treated by the oral administration of relatively large doses of solution of potassium arsenite.

2. Distinct improvement in the clinical and hematologic manifestations has occurred in each patient in from twenty to fifty days.

3. The induced remissions were characterized by reduction of the erythrocyte, hemoglobin and hematocrit values to normal or nearly normal, reduction of the basal metabolic rate to normal, increase in body weight, increase in strength and subsidence or disappearance of symptoms.

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5. Giffin, H. Z., and Conner, H. M.: The Untoward Effects of Treatment by Phenylhydrazine Hydrochloride, J. A. M. A. **92**:1505 (May 4) 1929.

6. Stockman, R., and Charteris, F. J.: The Action of Arsenic on the Bone Marrow of Man and Animals, J. Path. & Bact. **8**:443, 1903. Isaacs, R.: The Effect of Arsenic on the Maturation of Red Blood Cells, Folia haemat. **37**:391, 1928. Farley, D. L.: Depressed Bone Marrow Function from the Arsphenamines, Am. J. M. Sc. **179**:214, 1930. Forkner and Scott.[4a]

4. The remissions may be prolonged at least for several months by continuation of the medication in reduced amounts.

5. The method of administration of the drug and the untoward effects due to treatment with arsenic are discussed.

6. The administration of solution of potassium arsenite to patients suffering from polycythemia vera constitutes a safe and reliable method for the palliative treatment of this disease.

DIAGNOSIS OF OBSCURE CASES OF PERNICIOUS ANEMIA

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Occasions frequently arise when it is extremely difficult to make a diagnosis of pernicious anemia with absolute certainty. This difficulty has been enhanced since the discovery of the efficacy of liver [1] and other potent materials [2] because of the widespread tendency of physicians, before making every effort to reach a definite diagnosis, to treat all patients with anemia, and often patients with vague neurologic disturbances, as if they had pernicious anemia. The premature feeding of potent material will often so mask the natural course of the disease and the typical morphologic changes in the blood that two of the most valuable diagnostic aids will be lost.

The result of this tendency to treat anemic patients as patients with pernicious anemia naturally leads to a certain degree of uncertainty on the part of both patient and doctor, so that ultimately the treatment will be carried out half-heartedly, and the patient will thereby be subjected to the danger of development of neurologic symptoms because of inadequate therapy, or to unnecessary expense if the diagnosis is incorrect.

It is becoming more and more apparent that if patients are adequately treated and the blood maintained at a normal level, lesions of the spinal cord will develop in few, if any, of them.[3] There is likewise

From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

2. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. A. M. A. **93**:747 (Sept. 7) 1929. McCann, W. S.: Effect of Kidney on Blood Regeneration in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **15**:255, 1928. Ungley, C. C.: Effect of Brain Diet in Pernicious Anemia, Lancet **2**:63, 1931; ibid. **1**:227, 1932.

3. (*a*) Ungley, C. C., and Susman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effect of Liver Therapy, Brain **52**:271, 1929. (*b*) Baker, B. M., Jr.; Bordley, J., III, and Longcope, W. T.: The Effect of Liver and Liver Extract upon the Symptoms and Signs Referable to the Nervous System in Pernicious Anemia, Am. J. M. Sc. **184**:1, 1932. (*c*) Richardson, W.: Pernicious Anemia (Results of Treatment with Liver or Its Derivatives in 67 Cases), New England J. Med. **200**:540, 1929.

increasing evidence that if patients with changes in the cord are treated vigorously, many may have reasonable hope of improvement.[3b] Inasmuch as it often takes months or even years for signs of this improvement to appear, it is obvious that the discomfort and expense of taking massive amounts of potent material over such a long period is unwarranted unless an absolute diagnosis has been made.

To make a diagnosis of pernicious anemia is, as a rule, relatively simple, but occasionally it is necessary to resort to a therapeutic test. This entails a control period without treatment, followed by the administration of large amounts of potent material, with daily counts of the reticulocytes and of the red blood cells and an estimation of hemoglobin. Should the response of the blood be inhibited by infections, arteriosclerosis or chronic diseases of another nature,[4] an absolute diagnosis by this method may not be possible on account of an inadequate rise in reticulocytes and red blood cells. It is not uncommon, furthermore, to encounter patients with neurologic disturbances who have relatively little alteration in the morphology of the blood. When there is only moderate anemia, the examination of the blood smear may leave considerable room for doubt as to the diagnosis. In the majority of cases measurement of the mean volume of the red blood cells reveals a macrocytosis even when the anemia is slight,[5] and when this is associated with bilirubinemia and urobilinuria in a patient whose symptoms and signs suggest pernicious anemia, the latter is the likely diagnosis. Not only is it true, however, that in rare instances even these signs may be absent, but it must also be kept in mind that the discovery of macrocytic anemia in itself does not always signify pernicious anemia. Some instances have been observed in which signs and symptoms of disease of the spinal cord have occurred in association with macrocytic anemia in the absence of pernicious anemia.[6]

The diagnosis may be even more difficult in instances in which the patient has been receiving small amounts of potent material before coming under observation; as a result, the blood picture may so nearly approach normal that pernicious anemia will seem unlikely, and the patient will be discharged untreated. If, however, pernicious anemia is suspected, treatment with liver may be discontinued for purposes of diagnosis to ascertain whether or not the blood changes to the typical

4. Beebe, R. T., and Lewis, G. E.: The Maintenance Dose of Potent Material in Pernicious Anemia, Am. J. M. Sc. **181**:796, 1931.

5. Wintrobe, M. M.: Hemoglobin Content, Volume and Thickness of the Red Blood Corpuscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy, Am. J. M. Sc. **181**:217, 1931. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte, J. Lab. & Clin. Med. **17**:899, 1932.

6. Schumacker, H. S., and Wintrobe, M. M.: The Blood Picture in Cirrhosis of the Liver, to be published.

picture of the disease. This procedure is dangerous and time-consuming, however, for the blood may change very slowly, while changes in the cord may advance rapidly, just when the most vigorous therapy with potent material is indicated.

We recently encountered two cases which offered so much difficulty in diagnosis that it seemed necessary to resort to a special method of examination. Castle [7] showed that hamburger steak properly digested with normal gastric juice contains a substance capable of causing a remission in pernicious anemia. We employed this method for diagnostic purposes. Hamburger steak was digested with the gastric juice of the patients in question and given to two patients suffering from pernicious anemia who were having a relapse. The effect of this feeding was compared with that produced by giving hamburger steak digested with normal gastric juice.

METHOD

The patients to be treated were given 0.5 mg. of histamine sulphate subcutaneously every morning. The fasting stomach contents were then collected by means of a nasal catheter. The stomach excretion was small, but, by repeated aspiration, in the course of an hour from 50 to 75 cc. of gastric juice could be collected. Two hundred grams of hamburger steak, to which 4 Gm. of commercial pepsin had been added, was then brought by the addition of 2/3 concentrated hydrochloric acid to a p_H of 4.4. This end-point was determined by the pink color produced by the addition of a drop of the mixture to a drop of alizarin monosodium sulphonate solution. The mixture was then digested for two hours at 37 C. By the addition of concentrated sodium hydroxide the p_H was then lowered to 7.0, at which point the addition of a drop of the mixture causes bromthymol blue to become green. Seventy-five cubic centimeters of the gastric juice to be tested was added and allowed to incubate for two hours. It was then strained through a fine mesh sieve and given on six successive days by a nasal tube to a patient known to have pernicious anemia. The patients suffering from pernicious anemia who were to receive the mixture to be tested were first observed without treatment for a period of two weeks, in order to determine whether or not their blood remained at a stationary level. During this time reticulocytes were counted daily, and red cells and hemoglobin were determined twice a week. Patients with erythrocyte counts of less than 3,000,000 were selected as recipients of the mixture of hamburger steak and gastric juice, in order that a significant response of the reticulocytes and a rise in the blood count might be obtained. Ten or more days were allowed to elapse between the administration of the mixture to be tested and the material known to contain the intrinsic factor.

REPORT OF CASES

CASE 1.—A white man, aged 44, was admitted to the Johns Hopkins Hospital on Sept. 22, 1930. The history, physical findings and results of examination of blood were compatible with pernicious anemia, except for the presence of a small amount of free hydrochloric acid in the gastric contents. Following the oral

7. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. M. Sc. **178**:748, 1929.

administration of liver extract in large doses, the reticulocyte peak was only 4.8 per cent, although the red blood cells were 1,860,000. The blood later showed some improvement, but for two years the red cells did not rise above 2,500,000, in spite of the fact that the patient daily took the extract derived from 400 Gm. of liver. At this period he had a severe attack of phlebitis migrans, which left him with brawny edema of both legs, persistent fever and leukocytosis. This was followed by the gradual onset of changes in the spinal cord.

We felt that the diagnosis of pernicious anemia was warranted, and in view of the poor response to liver, it seemed necessary to give the patient massive amounts of potent material. Our plan was to give as much as 10 vials of liver extract no. 343 daily for one year. In view, however, of the presence of free hydrochloric acid in the gastric juice, the fever, leukocytosis, atypical response of the blood to feeding of liver and absence of papillary atrophy of the tongue, it seemed inadvisable to go to the trouble and expense of massive feeding unless the diagnosis of pernicious anemia could be definitely established. A section of sternal bone marrow was examined but was not found to be particularly abnormal.

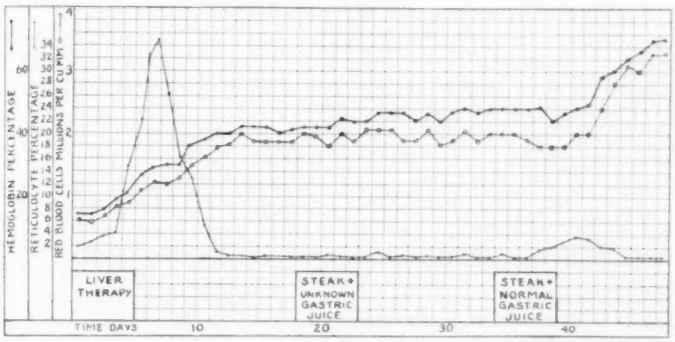

Chart 1.—Because of the extreme grade of anemia, this patient was first given sufficient liver extract to eliminate the danger. After an adequate delay, hamburger steak digested with the unknown gastric juice was administered. The ineffectiveness of this gastric juice is apparent when the lack of any change in the blood is compared with the small but definite rise in reticulocytes and the increase in red cells and in hemoglobin which followed the feeding of hamburger steak and normal gastric juice.

The patient's gastric juice was then tested by the method described, and was found to be inert as compared with the definite response obtained when the same amount of normal gastric juice was used in a similar manner (chart 1).

The subsequent course of the disease in this patient has proved beyond doubt that he is suffering from pernicious anemia. Intensive therapy for two years has maintained his blood at a normal level, and degeneration of the cord has not advanced.

The second case is of such interest that the history will be given in detail.

Case 2.—*History.*—A white man, aged 45, a university graduate, had been a good student. Until the illness under discussion began, he was considered a very intelligent man. His father died of paralysis at 45 years, but further details of

the illness could not be elicited. His mother died at 36 of pernicious anemia. One sister had some form of paralysis from which she recovered. Two sisters and one brother were living and well.

The patient's previous health had been excellent, with no illness of importance. He had been athletic and was a good tennis and handball player.

The present illness began about seven years before admission, when he noticed for the first time a tendency to easy fatigability. He began to lose his accuracy in tennis and handball. In the few years which followed he had many financial worries; he became nervous and tired. He had periods lasting several months when symptoms of fatigability and nervousness were much more apparent. During this time, however, he noticed no pallor, but gained weight and therefore eliminated from his diet milk, fat, cream, potatoes and bread.

Eighteen months before admission he became aware for the first time of numbness in his hands, which caused difficulty in writing. This was soon followed by such unsteadiness in his legs that it was necessary to discontinue his athletics.

Twelve months before admission his walking became much worse; he grew very unsteady, and his friends were aware of a diminution in his mental acumen. He saw his family physician, who reported that his blood was not particularly abnormal, but in view of the neurologic disturbances prescribed liver, which the patient took for two months. He then discontinued it, because he noticed no improvement.

Nine months before admission he was seen by a competent neurologist, who reported the following abnormalities: The tongue was slightly smooth, but not red. The cranial nerves were normal. There was no weakness or tremor. There was slight error in the finger to nose test, and the gait was slightly unsteady. The patient could not walk heel to toe, but the gait was spastic, not ataxic. There was numbness up to the wrists and the hips; cutaneous sensibility in this region was altered but not lost. Sense of passive movement and position of fingers and toes was diminished or lost. There were loss of two-point sense in the hands and loss of vibratory sense in the legs and slightly in the hands. The reflexes were slightly sluggish in the arms, but active in the legs. There was no clonus. The plantar and abdominal reflexes were sluggish. The reaction to the Wassermann test was negative. Roentgenograms of the gastro-intestinal tract showed no abnormalities. Gastric analysis showed no free hydrochloric acid and a total acid of 6 degrees. The red blood cells numbered 5,000,000; the hemoglobin was 100 per cent (14.5 Gm.); the white blood cells, 7,000, and the smear, normal.

The impression of the neurologist was that the condition was pernicious anemia, but because of the normal blood, he changed the diagnosis to multiple sclerosis, evidently overlooking the fact that the patient had been taking some liver for about three months before the examination was made.

The patient discontinued the liver nine months before admission, and for several weeks felt a great deal better. He improved to the point of being able to play tennis again, and his voice, which had become somewhat unsteady, became stronger.

Suddenly the disease began to advance rapidly. Spasticity progressed to the point of confining him to bed; his hands became very unsteady, and for the three months preceding admission he was unable to walk or write.

He was admitted for short periods to two other hospitals. In one he was thought to have multiple sclerosis, and was treated with a vaccine; and in the other he was thought to have pernicious anemia and was therefore treated with liver in small amounts for several weeks, without improvement. He was admitted to the Johns Hopkins Hospital on Jan. 21, 1932.

Examination.—On admission, the temperature was 99 F.; the pulse rate, 80; the respiration, 22, and the blood pressure 120 systolic and 80 diastolic. The patient was well nourished and cheerful, almost euphoric at times, and seemingly without insight into his condition. This mental change had been noted by the family during the year previous to presentation. Because of the great spasticity and contractures of his legs, he had become completely bedridden. There was a large amount of soft, flabby, subcutaneous fat, and the skin had a slightly yellowish color. The hair was prematurely gray. The mucous membranes showed slight pallor. The pupils and extra-ocular movements were normal. The fundi showed no definite abnormalities, except slight pallor on the temporal side of the left disk. Visual fields and visual acuity were normal. The retinal vessels were normal. The tongue was rather large and red, with slight but definite atrophy of the papillae at the tip and along the margin. The thyroid was just palpable. The heart and lungs were normal. No sclerosis of the peripheral vessels was evident. There were no palpable abdominal masses, and no edema or clubbing of the extremities.

Speech was at times a little slurred. The only demonstrable involvement of the cranial nerve was some deviation of the soft palate to the right on phonation, and absence of the gag reflex. There was diminution in the sense of pain below the third rib on both sides. This sense was practically absent below the twelfth dorsal vertebra on the right and the first lumbar on the left. Light touch could not be felt below the sixth dorsal vertebra. Vibratory sense was absent in the legs and spine up to the first dorsal vertebra and absent over both wrists and the right elbow. Sense of passive movement and position was lost in the fingers and toes, and diminished in the shoulders and elbows. There were slight weakness of all muscle groups of the arms, marked ataxia on the finger to nose and finger to finger tests, and marked adiadokokinesis, worse in the left hand than in the right. The legs were very spastic, with contractures, especially of the hamstrings on the left. Coordination could not be tested because of the contractures. There was no fibrillary twitching or muscular atrophy. All the deep reflexes were hyperactive, more so in the legs than in the arms. There were bilateral Babinski and Hoffmann signs. The abdominal reflexes were absent. Gait and station could not be tested, because the patient could neither stand nor walk. There was occasional loss of vesical and rectal sphincter control during the last months.

Laboratory Findings.—The urine was normal; urobilinuria was absent. Examination of the blood showed: red blood cells, 5,020,000; hemoglobin, 92 per cent (13.3 Gm.); white cells, 6,200; polymorphonuclears, 62 per cent; polymorphonuclear eosinophils, 1 per cent; polymorphonuclear basophils, 0.5 per cent; color index, 0.92; reticulocytes, 0.9 per cent; lymphocytes, 33.5 per cent, and monocytes, 3 per cent.

The smear showed moderate anisocytosis, with a number of macrocytes and rather numerous microcytes. One polychromatophilic cell was seen. The mean corpuscular volume was 83 cubic microns. Platelets were plentiful.

The Wassermann tests of the blood and the spinal fluid were negative. The Pandy and colloidal mastic tests also gave negative results. Gastric analysis after fasting showed: free hydrochloric acid, 0; total acid, 7.5 degrees; the histamine test (0.5 mg. subcutaneously) revealed: free hydrochloric acid, 0, and total acid, 2.5 degrees. The van den Bergh test of the blood showed an indirect trace. The icteric index was 12.

It was important to reach an accurate diagnosis in this case. In the first place, had it been possible to make a diagnosis of pernicious anemia a year previously, with proper treatment the patient might not have reached such a state of hopeless invalidism. Furthermore, since it is becoming increasingly evident that

the only way in which improvement, or at least the prevention of further advance of symptoms in the cord, can be expected is by the administration of massive amounts of potent material, our problem was to determine whether or not this patient should be subjected to the expense of such treatment.

As a final diagnostic proof, therefore, the gastric juice was tested as described in the preceding paragraphs. It was found to be impotent as compared to the control normal juice (chart 2).

With these data in hand it seemed logical to treat him vigorously, not that much improvement could be expected in such an advanced and long-standing case, but in the hope of preventing further progress of the disease. He was therefore given as much liver as he could take, which amounted to 500 Gm. of raw liver emulsion daily, and in addition 600 cc. of domestic liver extract made according to Castle's formula.[8]

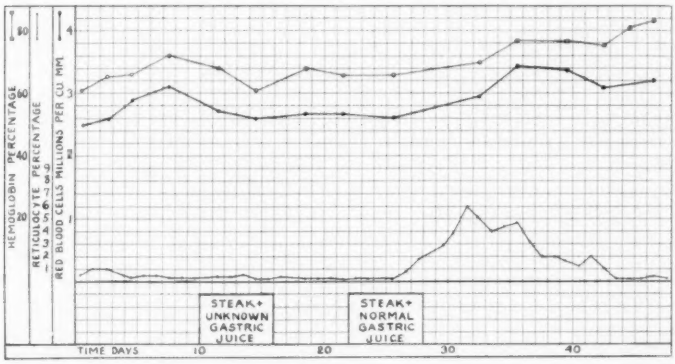

Chart 2.—No response of reticulocytes, red blood cells or hemoglobin followed administration of hamburger steak digested with unknown gastric juice. Good response of reticulocytes and rise in red blood cells and hemoglobin followed the feeding of normal gastric juice and hamburger steak.

As was expected, no rise in reticulocytes was obtained because of the high level of red blood cells and hemoglobin. The latter elements rose somewhat, and the patient soon felt and looked a great deal better.

The feeding of massive amounts of liver has been continued for six months. Although there is as yet no demonstrable improvement in the signs and symptoms due to the lesions of the nervous system, there has been no advance of the disease.

COMMENT

A question which arises at once is whether the absence of the "intrinsic factor" is confined to cases of pernicious anemia. Exhaustive studies on this subject have not been carried out. Castle reports

8. Castle, W. B., and Bowie, M. A.: A Domestic Liver Extract for Use in Pernicious Anemia, J. A. M. A. **92**:1830 (June 1) 1929.

that the gastric juice of patients suffering from idiopathic, microcytic anemia is effective in producing a reticulocyte response in pernicious anemia.[9]

Whatever observations may show in other conditions, there seems to be sufficient evidence at present to believe that in a patient whose signs and symptoms suggest pernicious anemia the discovery of the absence of the intrinsic factor in the gastric juice makes the diagnosis of pernicious anemia at least extremely probable.

SUMMARY AND CONCLUSIONS

Two cases are described in which it was not possible to make an absolute diagnosis of pernicious anemia by the usual methods of examination.

Castle's discovery of the efficacy of hamburger steak digested with gastric juice from normal persons in producing a remission in pernicious anemia was utilized to establish the diagnosis in these cases.

This was done by comparing the effectiveness of the gastric juice obtained from the patients in question with that of gastric juice from normal persons when fed to patients suffering from pernicious anemia.

Such a test is of assistance in confirming the diagnosis: (1) when, on account of infection, chronic disease of any nature and arteriosclerosis, the response to appropriate treatment is inadequate and leaves room for doubt as to diagnosis; (2) in cases of damage to the spinal cord and little or no anemia, when an absolute diagnosis cannot be made on the basis of the morphology of the blood or therapeutic tests, and (3) in patients with little anemia who are already receiving liver therapy and in whom cessation of treatment for the purpose of diagnosis might prove harmful and permit onset or advance of the damage of the spinal cord.

The importance of making a definite diagnosis early in the disease is emphasized, particularly in patients suffering from involvement of the central nervous system. In such cases, if the diagnosis is definitely established, vigorous therapy can be continued for many years, with the full confidence of both the patient and the physician that the diagnosis is correct, and that time and effort are not being wasted in treatment.

9. Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, Am. J. M. Sc. **182**:741, 1931.

Book Reviews

Entstehung, Erkennung und Behandlung innerer Krankheiten. By Ludolf Krehl. Volume 3. Price, 18 marks. Pp. 289. Berlin: F. C. W. Vogel, 1933.

It is impossible to review this book without considering its two companions, the first on pathologic physiology and the second on diagnosis. It is equally impossible to review the trilogy without reflecting on the author and on his peculiar aptitude for writing a complete textbook of medicine in the form he has selected.

Professor Krehl was born in 1861, and became a doctor of medicine when he was 25 years old. Subsequently he acquired an admirable medical training: first as Privat Dozent in Leipzig, then as professor of medicine at Jena—receiving the honor when he was only 31 years old—then as Professor at Marburg, Greifswald, Tübingen, Strassburg and finally Heidelberg. With an experience of such breadth, it is no wonder that Sir William Osler remarked of him in a preface to Hewlitt's second edition of the translation of the "Pathological Physiology" published in 1907, "The author has had the advantage of prolonged laboratory training to which has been added that accurate knowledge of disease to be had only by years of study and teaching in the wards."

The present volume may be said to owe its origin to a little book which first appeared in 1893 under the title of "Grundriss der allgemeinen klinische Pathologie." In 1898, its name was changed to the better known one of "Pathologische Physiologie," and ever since it has enjoyed a well deserved popularity. The thirteenth edition was published in 1930 as the first part of a new medical textbook, and was received with so much enthusiasm that a fourteenth edition was necessary in 1932. This section of the textbook has already been reviewed in the ARCHIVES, and can be recommended with unstinted enthusiasm to every one.

The second part of the series, on diagnosis, was off the press in 1931, and required a second edition in 1932. This section, too, has been reviewed in the ARCHIVES. The review speaks well of the volume and comments on the fact that it is obviously and refreshingly written by a single author, who thinks as he writes, is inclined to philosophize in an engaging manner on various medical trends as he has seen them develop in his experience and, above all, stresses the point of view that the good physician must strive continually to apply to the patient as an individual sample of humanity what is known of the science of medicine.

The third section, on treatment, has just appeared, and is in every way up to the standard of the rest of the series. As might be expected of a writer of the author's training, it is comparatively short: 289 pages against 716 pages on pathologic physiology and 192 pages on diagnosis. As is stated in the preface, it is not written for professors or men of that caliber, but for young German practitioners who are beginning. The general principles of treatment are well covered, as are the various forms of treatment to be used in ameliorating the symptoms of disease involving the special systems. Different kinds of treatment are discussed, such as the use of drugs, of surgery, of massage and of radiotherapy, hydrotherapy and psychotherapy. An admirable bibliography is appended to nearly every page, and almost all the references are to German writers. Presumably this is done by intention, since the book is written for the benefit of young German physicians who may be expected to read the German literature but who are less likely to read French or English easily.

The most appealing feature of Professor Krehl's book, however, regarding the three books as a single unit, lies in the fact that it is written by one man and from an individualistic point of view. It has been said that the rapid growth of medical knowledge during the last few years has made it almost impossible for a single person to master the entire field, and that the age of specialism has arrived. Professor Krehl refutes this argument. He has written a book which

covers the entire field of medicine, and which demonstrates a comprehensive knowledge of the subject. He expresses his personal views on all phases of medicine with clearness and force. He writes delightfully, so that the book as a whole moves along without bumps or jerkiness. He seems to have reaccomplished today what Niemeyer accomplished for German medical literature in 1858. Perhaps his example will inspire one of our modern American authors to make as equally a valuable contribution to the American medical literature as did Osler in 1892.

Lectures on Endocrinology. By Walter Timme, M.D., Senior Attending Neurologist, Neurological Institute, New York; Professor of Clinical Neurology, Columbia University (College of Physicians and Surgeons); Past President, Association for the Study of Internal Secretions and Association for Research in Nervous and Mental Diseases. Second edition. Price, $2.50. Pp. 192, with 38 illustrations. New York: Paul B. Hoeber, Inc., 1932.

In a rambling account, woefully antiquated, the author considers rather unscientifically the following glands; thymus, thyroid, pineal, parathyroid, suprarenal and pituitary glands and the gonads. For example: "Theoretically, the thymus secretes a substance which has vagotonic properties . . .; ammonium carbonate being converted finally into urea by parathyroid action." In the short section on hyperparathyroidism appears a final paragraph in which the author refers to the administration of parathyroid extracts, whereas in the first paragraph such administration is obviously contraindicated, since osteitis fibrosa cystica is shown to be due to a hypersecretion of the parathyroid glands. Such important topics as homeostasis and the tuberal syndrome are not even mentioned. Pitressin and pitocin are referred to as vasopressin and oxytocin—names long ago discarded. The recent interesting work on hebin is not even referred to; neither did the reviewer find a discussion of theelol, theelin, progestin or the purified preparations of the male sex hormone. There is little justification for a book of this type.

Anleitung zur frühzeitigen Erkennung der Krebskrankheit. By Best, Fromme, Payr, Rostoski, Saupe, Schmorl, Tonndorf and Warnekros. Second edition. Price, 3 marks. Pp. 134. Leipzig: S. Hirzel, 1932.

The first edition of this book was published in 1917. Very few copies came to this country, so that it is almost unknown here. It was written for the benefit of general practitioners not in a position to be especially familiar with cancer, and endeavored to give them easily digested information on the various ramifications of this subject. While it did not differ greatly from other books written for the same purpose and published in other parts of Europe at about that time, yet it was unusually comprehensive, well put together by a group of able writers, and did not contain information unsupported by known facts.

The second edition of the book has the same purpose and is written in much the same style. It has grown in size to keep abreast of the progress that has been achieved in the last fifteen years and so is forty pages longer. Several of the original authors have been changed, and now, with but one exception, they all come from Dresden. They write well and clearly.

In brief, the book gives an admirable summary of the various methods at present available for the early recognition and treatment of cancer. It is written simply and contains so much information on cancer of practical clinical value that, without doubt, the book will be of considerable use to the practitioners for whose benefit it has been written.

The Laboratory in Surgical Practice. By E. C. Dodds, M.V.O., M.D., and Lionel E. H. Whitby, C.V.O., M.D. (Camb.), M.R.C.P. (Lond.), D.P.H. Price, 8 shillings, 6 pence, net. Pp. 196. London: Constable & Co., Ltd., 1931.

This is a book that every practitioner of surgery or medicine would profit greatly by reading, if he has the patience to do so. Because of the nature of the

subject, it becomes laborious to read it through completely; hence, it must resolve itself in becoming a reference book, and, as such, it is excellent for the practitioner.

It is not sufficiently exhaustive for the pathologist or the laboratory man. It does coordinate the laboratory findings with the clinical picture and shows or reminds the clinician what future laboratory examinations should be made when certain pathologic changes are suspected, and how these findings should be interpreted.

Much of the first half of the book is given over to subjects that fall almost entirely within the realm of the clinical pathologist, but in the chapters on the kidney, stomach, gallbladder and liver and the thyroid gland, the authors, I believe, reached the objective of the book in making it a helpful laboratory manual for the surgeon. It is a valuable addition to any library.

An Index of Prognosis and End-Results of Treatment. By Various Writers. Edited by A. Rendle Short. Fourth edition, fully revised. Price, $12. Pp. 599. New York: William Wood & Company, 1932.

The fourth edition of this book appears ten years after the one that immediately antedated it. Since that time there has been a pronounced alteration in the outlook of such diseases as diabetes, pernicious anemia and nephritis, to mention only a few of the outstanding conditions that can be modified favorably by appropriate treatment. Necessarily, this has called for a revision of certain sections of the book. Except for these comparatively few changes there has been no radical alteration in the context of the book. It gives a complete summary of every conceivable type of condition which might cause death, arranged in alphabetical order. A minor criticism might be that there is a disproportionate amount of space given to some of the conditions, chlorosis, for example, being given somewhat over two and a half pages, whereas coronary thrombosis has about one page assigned to it. All in all, with the exception of a few trivial criticisms, the book can be highly praised. It represents well balanced, conservative statements by well qualified authors as to the future outlook of practically every disease to which man is heir.

The Heart Rate. By Ernst P. Boas, M.D., Associate Physician, Mount Sinai Hospital, New York, and Ernst F. Goldschmidt, Ph.D., Research Fellow (1930-1931), Department of Surgery, Yale University School of Medicine. Price, $3.50. Pp. 166, with 68 figures and 30 tables. Springfield, Ill.: Charles C. Thomas, 1932.

The present volume records a study of the heart rates of fifty-one normal men and fifty-two normal women by means of the cardiotachometer, a device which permits, within certain practical limits, a continuous record of the heart rate over twenty-four or more hours. With this instrument the heart rate was studied during waking and sleeping states. The data were correlated with certain body measurements. Furthermore, the cardiac rate was studied during certain daily activities. In chapters VII and VIII one finds studies on the pulse rate made during various types of anesthesia and in certain disease conditions (cardiac insufficiency, valvular disease, myocarditis, exophthalmic goiter, neurogenic sinus, tachycardia, auricular fibrillations and complete heart block). Chapter I contains a delightful historical account of the knowledge of the pulse rate from antiquity to the present time. The book is well written, and affords valuable data on the subject offered.

Elektrokardiographie für die ärztliche Praxis. By Prof. Dr. Erich Boden. Price, 12 marks. Pp. 160. Dresden: Theodor Steinkopff, 1932.

The disturbances of cardiac mechanism are a bugaboo to many physicians, and at the sight of a complicated looking electrocardiogram they frankly throw up their hands in despair. This state of affairs is not unintelligible, since simple and lucid expositions of the subject are difficult to find. Sir Thomas Lewis' "Mecha-

nism and Graphic Registration of the Heart Beat" still remains the great storehouse of information, but neither it nor the other smaller treatise on clinical electrocardiography seems to be widely read in this country.

This little book by Boden—if the American reader is not scared off by a foreign language—is an admirable elementary exposition of electrocardiography "for the actual practitioner." Outstanding features are the exquisite tracings and diagrams, which really make the understanding of the usual terrors such as "flutter," "ventricular tachycardia" and "nodal rhythm" simple, even for the most timorous. The author holds to conventional views, which might here and there be challenged by the special student, but perhaps in a work of this sort controversy had better be avoided.

Textbook of Medicine. Edited by J. J. Conybeare, M.C., M.D. (Oxon.), F.R.C.P. Second edition. Price, $7. Pp. 1,004. New York: William Wood & Company, 1932.

The general character of the book is the same as in the previous edition, there being sections on dermatology, pediatrics, tropical medicine, diseases of the nervous system and general medicine. Practically one fourth of the space is given over to the nervous system. There are four additional contributors, making a total of fourteen, but the editor contributes by and large the greater portion of the material. No orderly manner is followed in dividing the book into sections or divisions for the various authors. More space is devoted to physiology and laboratory procedure than is done in books of the same scope by American authors.

When it is realized how great a field the book attempts to cover, it is evident that the subject matter must be very limited and in many instances must reach the proportions of an outline. Possibly it may have a place in the library of the general practitioner, but it can meet with little favor as a textbook.

Die Praxis der Grundumsatzbestimmungen. By Viktor Niederwieser. Price, 4.20 marks. Pp. 61. Berlin: Julius Springer, 1932.

This booklet presents the results of determinations of the basal metabolic rate made by the author on hundreds of patients, in different age groups and under varied conditions, together with copious citations from the literature. The main points of interest are the rates obtained following the administration of medicaments, physical therapy and therapy with various rays, as well as sunlight, and those obtained during acute and chronic infections, disturbances of the internal secretions, pregnancy, tumors and a few psychoses.

Unfortunately, many of the findings are either contradictory or inconclusive, with perhaps the exception of those obtained during the exposure to sunlight or ultraviolet rays and others made on patients with hyperactivity or hypo-activity of the ductless glands. The material is well arranged and well presented, and the brochure as a whole is quite readable and instructive.

An Index of Treatment. By Various Writers. Edited by Robert Hutchinson, M.D., F.R.C.P. Tenth edition, revised. Price, $12. Pp. 1,027. New York: William Wood & Company, 1931.

Belittle, if you will, an attempt adequately to cover the entire field of therapeutics in a single volume, but here is a nearly successful attempt. In scope and quality, there is no comparable American text. Its list of contributors reads like a section of a British "Who's Who in Medicine." Modestly promising only to provide the practitioner with a guide to treatment within moderate compass, one marvels at the completeness and amount of detail. Eschewing fads and recommending conservative but also eclectic methods, each author attempts to give what he thinks is the most logical treatment of the disease he is considering. Perhaps more noteworthy than the undoubted excellence of each contribution are the amount and variety of topics, which range from ingrowing toe-nails to hypnotism, from corns and bunions to dysparemia, from gunshot wounds to Dhobie's itch, from transfusions to electrotherapeutics.

Physical Chemistry for Students of Biology and Medicine. By David I. Hitchcock. Cloth. Price, $2.75. Pp. 182. Springfield, Ill.: Charles C. Thomas, 1932.

Dr. Hitchcock presents discussions of many of the fascinating aspects of physical chemistry which have come to have direct applications to medical and biologic problems: membrane equilibria, enzyme action, equilibria in blood, the colloidal state, etc. While the handling of the subject is in a sense elementary and hence an old story to the expert, the criticism may be made that the reasoning is not developed in enough detail to make matters clear to the average physician or medical student. Over and over again one comes face to face, unexpectedly, with quite complicated mathematical formulas, evidently of obvious simplicity to the writer, but difficult for the reviewer. Perhaps some one can be persuaded to write as a prelude to this book another one in which the necessary mathematics is developed.

Polyposis Gastro-Intestinalis. By Hans Tønnesen. Pp. 224. Copenhagen: Arnold Busck, 1931.

Based on a collection of Danish cases, the author gives a systematic discussion of gastro-intestinal polyposis. The material is handled in a thorough, yet simple manner, and while nothing fundamentally new is brought out, the monograph covers existing knowledge of the subject in an adequate way. The illustrations are excellent. The text is in German.

CORRECTION

In the article by Drs. Robert C. Moehlig and Gaylord S. Bates, entitled, "Influence of the Pituitary Gland on Erythrocyte Formation," in the February issue of the ARCHIVES (**51**:207, 1933), the third line on page 221 should read "13. Nerve end corpuscles," and "2 cm." in the seventh line on page 227 should read "2 mm."